The Hygiene Hypothesis and the Primary Prevention of Allergic Diseases

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Abstract

It has been suggested that there has been an increase in atopy and allergic diseases over the last 30 years; these diseases include allergic rhinitis, atopic asthma, and atopic dermatitis. Multiple explanations have been proffered to explain the increase in atopy and related diseases with the hygiene hypothesis the front-running theory. Before addressing the mechanism of the increase in such atopic diseases, it must be questioned whether allergic diseases have really increased. When isolating atopic asthma as the disease of interest, it is unclear whether or not there has actually been an increase in incidence of this disease.

INTRODUCTION

The best study to determine whether a population had an increased incidence of asthma over time would be one that used an identical definition of asthma over time, studied the same population over serial birth cohorts over time, and determined the incidence as well as prevalence of asthma in each successive cohort. No such study has ever been done. Any other study design would always be fraught with many potential interpretation problems. One review attempted to evaluate the literature to determine whether or not there was a secular trend in the occurrence of asthma in children and young adults ([1]). This analysis came to the conclusion that there was no solid evidence for an increased prevalence (and presumed incidence) of asthma. This was despite the fact that all the studies cited in the review felt there was an increased prevalence of asthma. The weakness of 15/16 studies was related to having no objective measurement that increased. However, increasing public and physician awareness of asthma, changing definitions of asthma, more specialization in lung and allergic diseases with resultant detection of many otherwise occult cases, and more testing for atopic diseases has changed the landscape for the diagnosis of allergic diseases including asthma. In addition, more developed countries will have a higher incidence of asthma and allergic diseases secondary to less developed countries due to better availability of health care services that are also more advanced. All these factors have increased the diagnosis of asthma and taken a disease that was under diagnosed ([2]) and made it much more prevalent. The same can be said of the other allergic diseases, atopic dermatitis and allergic rhinitis and atopy in general. It must be remembered that a diagnosis of atopy depends on the number of skin tests placed. The more skin tests placed the greater the prevalence of atopy.

Given no definitive convincing evidence for an increase in asthma or other allergic diseases, what can be said about the hygiene hypothesis in explaining these diseases even if they have only become more prominent with no increase in prevalence? It is well known that children are born with a predominant Th2 cytokine profile ([3]). Within the first 5 years of life ([4]), and most probably in the first two years of life ([5]), immune deviation occurs resulting in the majority of subjects developing a more balanced Th1/Th2 cytokine response. In subjects without immune deviation, the Th2 response persists and the patient becomes atopic and more prone to allergic diseases. It is unclear whether this occurs as a programmed event related to genetic background or secondary to immune deviation due to antigen exposure in the first few years of life. The only thing that is certain is that subjects who become atopic do not undergo immune deviation and subjects who do not develop allergic disease are less atopic and undergo immune deviation.

The Hygiene Hypothesis states that there is an increase in world-wide allergic disease, more marked in developed countries, that is secondary to a lack of many viral and bacterial infections that used to occur in the first two years of life. Vaccinations, early use of antibiotics, the use of

pasteurized milk instead of unpasteurized milk (teeming with micro-organisms), and an industrialized lifestyle with less children result in less exposure to infectious agents and less stimulation of the immune system to release interleukin-12 and interferon gamma, both needed to stimulate a Th1 cytokine response with simultaneous suppression of the Th2 cytokine response. This transition from a Th2 to a Th1/Th2 cytokine response is called immune deviation and needs to occur; if this response does not occur, then the Th2 response remains predominant with atopy and a predisposition toward the development of allergic diseases.

The origin of the Hygiene Hypothesis came from a study by Strachan in 1989 ([6]). He studied the epidemiology of hay fever and eczema in 17, 414 British school children from birth to age 23. Three outcomes were investigated; self reported hay fever at age 23, parental report of hay fever or allergic rhinitis at age 11, and parental recall of eczema in the first year of life when the child was seven. The data clearly show to the untrained eye that the prevalence of both allergic rhinitis and eczema are reduced as the number of older siblings in the household increase. These results were independent of the social class of the father. In order to explain the striking results, Strachan postulated that the protective effect of older siblings and siblings in general was related to increased infections with larger family size that reduced the expression of atopy in some way. Now, with declining family size, greater personal cleanliness, and affluence with less crowding, the opportunity to develop these infections is reduced resulting in a greater prevalence of allergic diseases.

This theory has held up in subsequent studies clearly showing that the sibling effect, whether related to the home environment or exposure to day care in the first 6 months or year of life relative to later, reduces the likelihood of developing asthma and other allergic diseases ([7,8,9,10,11]).

INFECTIONS AND ALLERGIC DISEASE

A prospective birth cohort study from birth to age seven attempted to determine whether different infections in the first years of life resulted in a doctor diagnosis of asthma at age seven ([12]). The study found a striking protective effect of repeated viral infections other than lower respiratory tract infections in preventing asthma (odds ratio 0.31; 95% C.I. 0.11-0.85) in the first three years of life. Protective infections included viral infections resulting in rhinitis and viral infections of the herpes type. Repeated lower respiratory tract infections in the first 3 years of life showed a positive association with wheeze up to age 7 (odds ratio 3.37; 95% C.I. 1.92-5.92) for greater than or equal to 4 infections versus less infections. The study concluded with the idea that certain viral infections not related to lower respiratory tract were consistent with the Hygiene Hypothesis. Interestingly, it has been speculated that lower respiratory tract infections that occur early in life might cause significant damage or developmental problems to the tracheobronchial tree resulting in a predisposition toward developing asthma.

Due to suggestions from cross sectional studies that multiple febrile illnesses (ie systemic infections) in the first year of life were associated with a reduction in allergic diseases ([13,14]), a prospective birth cohort study evaluated the relationship between febrile illnesses in the first year of life and atopy and allergic asthma at age 6 to 7 ([15]). The febrile illness had to be documented in the office or hospital setting and not by history. This most likely resulted in an underestimation of the total number of febrile illnesses in the first year of life. The study found a reduction in allergic sensitization of 45% (odds ratio 0.55; 95% C.I. 0.31-0.97) with febrile URI and no reduction with nonfebrile URI. There was also a significant reduction in atopic asthma with febrile illnesses in the first year of life. Interestingly, there was a nonsignificant increase in atopy in children at age 6 to 7 with febrile LRI. This finding was not addressed specifically by the authors but is consistent with the previous finding that early LRI may be associated with an increased propensity for developing asthma ([12]).

Studies have shown a difference in maturation of the immune response in atopic versus nonatopic children followed from birth until age 2 or 3 ([5]). In particular, it appears as if children with a delay in Th1 responses early in life are more prone to lower respiratory tract infections that predispose to the subsequent development of asthma and atopy ([5,16,17,18]). A major question to answer is whether or not the lack of immune deviation that occurs in atopic children is inevitable or whether immune deviation can be encouraged secondary to recurrent stimuli early in life, presumably infectious agents. A second question would be, does immune deviation occur automatically in infants from nonatopic parents or would a lack of immune stimulation early in life promote an atopic child from nonatopic parents. If, in both groups of infants, appropriate immune stimulation early in life would promote immune deviation, and presumably a balanced Th1/Th2 lymphocyte immune response, then at least theoretically the primary prevention

of allergic diseases could occur.

PRIMARY PREVENTION OF ASTHMA

Have there been randomized studies that suggest that prevention of allergic diseases is possible? From the perspective of asthma there have been no successful studies that have tested the Hygiene Hypothesis to determine whether or not stimulation of immune deviation would result in primary prevention of asthma. One series of studies took infants at high risk of atopic disease and randomized them to environmental control of allergens versus no environmental control and evaluated atopy and associated diseases from the baseline of birth to 1, 2, 4, and 8 years ([19,20,21,22]). Although there was a reduction in atopic diseases at one year ([19]), there was no difference in allergic diseases between groups at 2 and 4 years old ([20,21]). At age 8, there was a significant reduction in atopy and skin test positivity to house dust mite and a mild almost significant reduction in asthma (odd ratio 0.11; 95% C.I.0.01 to 1.02) in the intervention group ([22]).

A second group of investigators also used environmental control measures prenatally and at birth to determine whether or not asthma and atopy could be reduced in children ([23, 24]). At the 3 year mark no explicit benefit has been demonstrated but further follow-up is needed to finally determine if asthma and atopic diseases will be reduced.

Finally, a third group of investigators randomized prenatal women to environmental intervention versus none and found a reduction in wheezing and rhinitis in children at one year in the intervention group ([25]). Obviously, continued follow-up is being done to determine if this effect will hold-up.

These results, although inconclusive at present, possibly suggest that allergen avoidance early in life might possibly decrease atopy and allergic diseases to some extent. None of these attempts at preventing the development of asthma have tested whether or not the presence or absence of intense microbial stimulation early in life reduces asthma prevalence.

PRIMARY PREVENTION OF ATOPIC ECZEMA

One study evaluated whether or not a probiotic in the form of Lactobacillus GG, given to mothers just before delivery and for 6 months after and to infants for 6 months after delivery if they were not exclusively breastfeeding, would prevent atopic disease by two years ([26]). The study was randomized and resulted in 15/64 developing atopic eczema in the treatment group versus 31/68 in the placebo group, a significant reduction in disease. The number needed to treat to prevent one case of atopic eczema was 5, implying if the prevalence of atopic dermatitis was 10% a reduction to 8.0% might be possible. The only inclusion criteria was a family history of atopic disease in one or more family members ie mother, father, or sibling. This unequivocal study was consistent with the Hygiene Hypothesis which also suggests that the appropriate gastrointestinal bacterial flora are needed to prevent allergic disease and cause immune deviation. It has been shown that allergic children are colonized with different gastrointestinal bacteria and less lactobacilli than nonallergic children ([27]). Possibly, the correct early microbial stimulation of gut associated lymphoid tissue may also be a way to prevent atopic diseases.

PROOF OF THE HYGIENE HYPOTHESIS

In order to facilitate understanding regarding the theory behind the hygiene hypothesis and studies designed to prove or disprove it, it is sometimes helpful to have a logical a priori set of guidelines to follow to maximize the probability of obtaining a definitive answer to questions asked. One helpful set of guidelines was suggested by Kemp and Bjorksten ([28]). These guidelines are:

1. The study is prospective.
2. The study demonstrates a reduction in atopic disease.
3. The study demonstrates a reduction in allergic sensitization or atopy.
4. Reasonable alternative explanations are unlikely.
5. The exposure of interest occurred in early life, ie presumably in the first two years of life.
6. The dominant immune stimulation during the study was Th1.
7. There is evidence of immune deviation from a Th2 to a balanced Th1/Th2 immune response or immune deviation occurred.

Given the above guidelines, one of the specific gaps in current knowledge regarding proof or disproof of the hygiene hypothesis is related to showing that a) the baseline state of the neonate is predominantly Th2, b) infections occurred in the first two years of life, c) immune deviation occurred after birth and within the first few years of life, d) immune deviation was in the temporal sequence consistent

with an increased total infection rate in the first few years of life. One elegant and specific study demonstrated that atopic children started out with Th2 responses and maintained them whereas nonatopic children started out with the Th2 responses that were suppressed somewhere around one year of age ([5]). However, it is unknown whether the two responses seen are genetically pre-programmed or can be influenced by microbial stimulation. This needs to be demonstrated in some way.

The largest factor predisposing to atopic disease is having a genetic risk. One potential study design might attempt to find children who have a positive family history of atopic disease from mothers with no other children and randomize them at birth to free day care for the first year of life versus none. Baseline neonatal Th1 and Th2 immune function could be obtained as well as similar immune function at 3, 6, 12, 18, and 24 months. The children would be at high risk for the development of atopic disease and presumably more infectious diseases would occur in those exposed to day care. A secondary exposure (primary intervention is day care, yes or no) that would be important to measure would be documented febrile episodes in the first year of life ([15]). Early febrile episodes have been associated with less allergic sensitization ([15]). In addition, documented infections can be determined during the different visits to see if total number and type of infections makes a difference in outcome ([12]). The primary outcome variables determined after age 6 would be the presence or absence of atopic disease as determined by skin testing and clinical parameters.

This type of study should hit all the points elucidated above and then some. In other words it would be:

1. Prospective, eliminating time sequence issues and recall bias (29).
2. Attempt to measure a reduction in atopic disease, if present.
3. Attempt to demonstrate a reduction in allergic sensitization.
4. Reduce the possibility of alternative explanations for the outcome due to its prospective and randomized nature.
5. Determine the exposure of interest in early life.
6. Determine the dominant immune stimulation via methods of reference 5.
7. Demonstrate whether or not immune deviation occurred and was related to febrile illnesses and recurrent infections.
8. Minimize confounding (29) due to the randomized nature of the study.
9. Determine whether or not the high risk of genetic predisposition toward allergic disease can be overcome by environmental manipulation (day care exposure, in this instance).

An n of 100 randomized 50 to each group would probably be fiscally sound as well as implementable in a city with a large population. The hardest part would be waiting to age 6 to 7 to do the final testing to determine the results.

FINAL COMMENTS

The hygiene hypothesis is currently at the forefront in postulating why allergic diseases occur or do not occur. Although it not clearly proven that allergic diseases have increased over the last 30 or more years (vide supra), it is possible they have since even anecdotal reports suggest that adults coming from other countries without allergic diseases often develop them while living in the U.S. This would suggest adult acquisition of allergic diseases related to environmental conditions present in the U.S., a different set of issues either intertwined with or separate from the hygiene hypothesis. Independent of whether or not allergic diseases are increasing, the sibling effect related to allergic diseases appears invariant in most studies and works in well with possibilities related to the hygiene hypothesis. Therefore, something appears to occur in early life that protects some siblings in large families from developing allergic diseases. The hygiene hypothesis may or may not explain what occurs, and deserves testing. If the hygiene hypothesis is correct, this leads to the exciting possibility of primary prevention of allergic diseases. This would truly be a breakthrough and would markedly decrease morbidity and mortality in a large percentage of the population.

Finally, it should be remembered that the immune mechanisms presented here are very simplistic and will not reflect the final immunology determined in the future. This should not prevent the experimental approach from determining whether or not the hygiene hypothesis is correct. If correct, possibly our young children will take pre- or probiotics prior to playing in the mud. Maybe we should eat dirt ([30]).

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