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Historical Articles

Infection, allergy and the hygiene hypothesis: historical perspective

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Abstract

The 'hygiene hypothesis' was popularized in the late 1980s to explain the high prevalence of atopic disorders in the developed countries. It links atopic disorders and the lack of early life infections. An association between the two is not novel and dates back to the beginnings of allergy, immunology and microbiology. Allergy and infection have always been closely related and the study of one has often provided new insights into the pathobiology of the other. Early research into bacterial infections led to the discovery of the human immune system and the concept of allergy. An important relationship exists between parasite infections and the development of atopic disorders.

This review traces the long and intimate historical relationship between infection and allergy.

Key words: Allergy and Immunology; Helminths; Parasites; History of Medicine, 20th Cent

Introduction

The 'hygiene hypothesis' was popularized in the late 1980s to explain the high prevalence of atopic disorders in the developed countries. It links atopic disorders and the lack of early life infections. An association between the two is not novel and dates back to the beginnings of allergy, immunology and microbiology. This review traces the long and intimate historical relationship between infection and allergy.

Origins of allergy from microbiology

In the late 19th century, the discipline of microbiology was established with the rapid increase in isolation of human bacterial pathogens. Subsequent discovery of natural antitoxins and the development of toxoid vaccinations shortly thereafter helped to establish the fundamental concepts of Immunology. It was not long before it was discovered that the human immune system was not wholly protective but could itself cause disease to the host. The concepts of hypersensitivity and allergy were introduced in the early 20th century.

Eosinophils and helminths

The discovery of the eosinophil and demonstration of its presence in both allergic disorders and helminth infestations provides another historical link between allergy and infection. Ehrlich described the eosinophil in 1879 when he observed that certain cells containing numerous intracytoplasmic granules stained strongly with the acidic dye eosin.[1] Soon after, Muller and Rieder noted significant eosinophilia in hookworm infections and others described numerous eosinophils in the sputum and blood of asthma patients. Prompted by these observations, Herrick (1913) quoted that 'Common to both bronchial asthma and *Ascaris* infestation is an increase of the eosinophils of the blood. One day we'll ask the significance of this eosinophilia in this association'. Herrick may have been the first to recognize an association between asthma and helminthiasis, and to question the significance of this relationship. Unfortunately, over a half-century was to pass before this potentially important link was seriously investigated.

Two groups working independently in Sweden and USA discovered IgE in 1967, and demonstrated its prominent role in both helminthiasis and allergic disorders.[2] Several studies in the 70s showed asthma to be uncommon in the tropics. Godfrey investigated the prevalence of asthma in Gambia where the population is heavily infected with helminths and failed to find any cases of asthma.[3] Similar results were obtained from studies in Rhodesia[4] and Papua New Guinea.[5] A recent meta-analysis of the data from these early surveys by Masters *et al.*[6] showed that, despite the variation in methodology, the prevalence of parasitic infections was negatively associated with the prevalence of asthma and allergic

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disorders. Supportive anecdotal example of such a link was provided by Turton in the *Lancet* (1976), who recounted how his longstanding hay fever did not recur after he had infected himself experimentally with hookworm.[7]

Although both IgE and eosinophils were prominent in both disorders, the underlying factor linking these two entities remained elusive. Two main areas of research developed. Many investigated the role of eosinophils whilst others studied the role of IgE in an attempt to understand and explain the precise relationship between helminthiasis and allergy. Investigators considered initially that eosinophils degraded mast cell mediators, and their removal ameliorates the allergic process. However it soon became apparent that eosinophil granules were toxic for helminth larvae, and by the 1980s eosinophils were shown to cause the tissue damage seen in asthma and related allergic diseases. Over the last 20 years, as more data accumulated, the picture is both more complex and more confusing. Eosinophils may be pluripotential, and depending on the circumstances, display distinctly differing roles in various physiological processes, including tissue homeostasis, host defence and tissue damage.

High IgE levels are seen in both helminth infections and atopic disorders. Johansson *et al.* also demonstrated,[8] that saturation of mast cells by the high levels IgE seen in myeloma patients inhibited the Prausnitz-Kustner reaction. These observations suggested that the paradoxically high IgE levels seen in parasitic infections prevent atopic diseases developing in such patients. Helminth-infested subjects are somehow protected from mast cell degranulation and inflammation by other allergens. The IgE blocking hypothesis explained this. An editorial in the *Lancet* in 1976, proposed that 'one theoretical approach to prevention or treatment of allergic diseases would be deliberately to induce high IgE responsiveness, for example, by artificial infection with parasites'. Immuno-epidemiological studies have shown the protection by helminth infections to be conferred by the high levels of polyclonal IgE.[4,9] Patients lost their skin reactivity to allergens following helminthic infections.

Hygiene hypothesis and Th1-Th2 theory

Epidemiological studies have shown a significant increase in the prevalence of allergic diseases in the developed world in the past two decades, which is not reflected in the developing countries. There are also clear differences between rural and urban areas within some countries. Numerous environmental factors associated with industrialized and urban living have been studied in an attempt to explain these differences but with little consistency except childhood infections. The number of early childhood infections is overwhelmingly and negatively associated with atopy. These may have a protective effect against atopic disorders. Matricardi *et al.*[10] showed that childhood exposure to food and oro-faecal pathogens, such as hepatitis A, *Toxoplasma gondii* and *Helicobacter pylori*, reduced the risk of atopy in later life by more than 60 per cent. David Strachan observed a higher prevalence of atopic allergic disease in first born children compared to their younger siblings and on the basis of this and other studies introduced the term, 'hygiene hypothesis', in 1989.[11] He proposed that lack of antigenic stimuli, because of improved hygiene, vaccination, and antibiotic use, could alter the human immune system such that it responds inappropriately to innocuous environmental substances.

Mosmann and colleagues[12] discovered that fully differentiated mouse CD4+ T cells secreted one of two different sets of cytokines, Th1 (e.g. INF-γ and Il-2) and Th2 (e.g. Il-4 and Il-5) cytokines which determine the direction of the inflammatory response. T-lymphocytes were stimulated by a normal granulomatous inflammatory response to produce Th1 cytokines. Most bacterial and viral infections have been shown to induce a profound Th1 response.[13] Lymphocytes producing Th1 cytokines suppressed the development of cells secreting Th2 cytokines; Th2 cytokines are associated with atopy and asthma development. The Th1 cytokines are viewed as the 'good' cytokines, which inhibit atopy immunopathology whereas Th2 cytokines are seen as the 'bad' cytokines. This important concept of the balance between the Th1 and Th2 responses has been pivotal for the hygiene hypothesis.

More recent research findings have supported the Th1-Th2 theory of atopy development and have provided further clues to the aetiologic factors responsible for an adverse Th1-Th2 balance associated with subsequent atopic disease development. The neonatal and early childhood periods are believed to be the critical periods for the establishment of the Th1-Th2 balance. These early infections are believed to establish a Th1-biased immunity and prevent the induction of the pro-allergic Th2 system. The intestinal microflora in infancy may be a source for the induction of immune deviation and the composition of the flora may determine who will and will not develop allergy disorders. Bjorksten *et al.*[14] studied newborns from two countries with differing allergy prevalence, Estonia and Sweden, for the first two years of life and demonstrated that in comparison with healthy infants, babies who developed allergy were less often colonised with enterococci, bifidobacteria and bacteroides in their stool cultures. Allergic infants had higher counts of staphylococcus aureus and clostridia counts. Several studies[15,16] have demonstrated that exposure to farming environments confers protection against allergy development. Von Mutius *et al.*[15] showed that this protective exposure to farm environments was most beneficial in the first six months of life and the effects are further enhanced if exposed for a prolonged period until the age of five years old.

Others have suggested that endotoxin exposure in early life confers protection against atopy development by stimulating Th1 responses.[17,18] Recently Bottcher *et al.*[18] studied infants from two countries which have a low (Estonia) and a high (Sweden) prevalence of allergy. They were able to demon-

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strate that endotoxin levels were higher in Estonian than in Swedish house dust. This may account for the observed difference in atopy prevalence. Furthermore, the levels of endotoxin inversely related to the development of atopic disease.

The hygiene hypothesis and developing immunological model have been very influential in directing strategies to prevent allergic diseases. In an attempt to redress the reduced microbial exposure in early life suggested in the hygiene hypothesis, probiotic administration in infancy has been studied. Probiotics are cultures of potentially beneficial bacteria of the healthy gut flora. Kalliomaki *et al.*[19] performed a randomised controlled trial using Lactobacillus GG in prenatal mothers and newborns. The frequency of atopic eczema in the probiotic group was shown to half that of the placebo group. Probiotics may prove to be effective method of atopy prevention. Using bacterial products to induce Th1 stimulation may prove effective against atopy development. Heat-killed Mycobacterium vaccae (SRL 172), a potent down-regulator of Th2 cytokines and stimulator of Th1 response, has been shown to prevent allergic manifestations in mouse models and suppress asthma during allergen challenge.[20] A recent randomised controlled trial has demonstrated M vaccae use to reduce allergen-induced airway responses in adult asthmatics.[21] These findings open up possibilities for new therapeutic interventions.

Other theories

Studies involving helminth infections have suggested that the Th1-Th2 model may be too simple. Helminth infections resolved in mice when Th1 cytokines were produced whereas an exacerbation occurred when Th2 cytokines were produced.[14,15] Later clarification established that helminth infections were associated with the most potent Th2 cytokine responses.[16] A major discrepancy in the hygiene hypothesis is that, although helminth infections and atopic diseases are associated with similar immunological phenomena, allergic responses were rarely observed in infected individuals. Rather, in contradiction, they are protected from allergy diseases. As a consequence, there has been some re-evaluation of the immunological basis of the hygiene hypothesis and various adaptations and new theories have been forwarded to explain this and other theoretical discrepancies.

The 'modified Th2' response

Asymptomatic helminth infections are correlated with high levels of IgG4, another Th2 dependent isotype, and it has been shown that these parasite specific IgG4 antibodies can inhibit IgE-mediated degranulation.[17] Originally, the concept of 'blocking antibodies' was proposed as a possible mechanism of allergen immunotherapy in the 1930s and 40s by Cooke, a pioneer of early immunotherapy. One of the characteristics of successful immunotherapy is the induction of allergen-specific IgG4 antibodies.[26] Platts-Mills *et al.*[27] showed recently that a high exposure to cat allergens results in high IgG4 titres and decreased atopy, supporting the role of IgG4 mediated down-regulating allergic responses. They proposed a modified Th2 response to explain the contradictory protective Th2 response seen in helminth-infested patients.

Education of the immune system by pathogens

A corollary of chronic parasite infections in humans is T-cell hypo-responsiveness. Helminth infections are associated with poor T-cell responses. This hyporesponsiveness is believed to spill over to unrelated antigens. Work on immunological responses to a purified protein derivative of TB, or tetanus toxoid after BCG, or tetanus vaccination has shown that responses are weaker in patients with concurrent helminth infection, as compared with healthy controls.[28,29] The immune system is educated towards an anti-inflammatory network by the chronic pathogen exposure with down-regulatory molecules such as IL-10 and TGF-B being implicated.[30] Immunosuppression with raised IL-10 levels has been shown in recent studies on filarial and schistosomiasis patients in Gabon.[31] Programming of the immune system in populations exposed to a multiplicity of chronic helminth infections may be quite different from those in subjects living in industrialized areas, where infections have been more successfully controlled. This may have important implications for the expression of immune-related diseases, such as allergy. Presence of a strong anti-inflammatory regulatory network, having been exposed to multiple childhood infections, could help inhibit the cascade of events leading to allergic inflammation.

Other types of infections have also been associated with the down-regulatory anti-inflammatory responses. Recently, studies on malaria, measles and tuberculosis have shown inverse association with atopy and each of these diseases was associated with immunosuppressive responses mediated by IL-10 or TGF-B,[32] and so the type of infection is not a critical factor. Although helminths induce the type-2 response, and virus and bacteria skew toward the type-1 response, the high overall infection burden seems to be the instrumental factor in the development of the anti-inflammatory regulatory network. This model questions whether certain pathogens carry signature molecules that are potent inducers of regulatory cells and thus protect from atopy. Instead of the Th1-Th2 dichotomy, a pro- versus anti-inflammatory T-cell regulatory axis may be central to the outcome.

Evolutionary by-product

It is possible that the human immune system evolved the immediate-type hypersensitivity to respond primarily to a wide variety of parasites present in the environment. Parasites may not directly prevent atopy but the removal of the parasites leaves an evolutionary-conserved mechanism without its usual target antigen. The IgE response to the common aeroallergens is then a default response in the absence of helminth and other parasite infections. This theory is consistent with the observed dissocia-

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tion between very high IgE levels and reduced or non-existent skin test reactivity to aeroallergens seen in those from areas infested with helminths. Perhaps the high IgE levels bind to mast cell receptors and block the actions of aeroallergen.

A broader paradigm

Although it is clear that variations in early life environment, such as childhood infections, pose significant risk factors for the development of asthma and other allergic disorders, many feel these are not sufficient to cause asthma by themselves. An evolving paradigm for allergy development considers postnatal risk factors, such as infections, to be only part of a greater scheme that includes fetal development and genetic predisposition. The idea that fetal programming can have a significant effect on subsequent development of chronic illnesses was popularized by Barker *et al.*[33] A prominent example of this is the increased risk of asthma and atopy seen in low birth weight infants. While Barker focused on fetal nutrition as the main factor, other factors are also important. Maternal environment during pregnancy, including infections, has been strongly associated with subsequent asthma and atopy development. If the result of the interactions between genetics and the in-utero environment is a skewed Th2 immunophenotype in the neonate, these infants are more likely to develop allergic disorders.[34]

Bacterial superantigens

The role of superantigens in atopic dermatitis provides a further link between atopic disorders and infections. Research into atopic dermatitis revealed that food and inhalant allergens played a triggering role in a subset of atopic dermatitis patients. This led to a search for other pathogenetic and triggering factors in atopic disorders.

Leyden and coworkers[35] noted in 1974 that *Staphylococcus aureus* was isolated from the skin lesions of more than 90 per cent of atopic dermatitis patients. The significance of this was recognized in 1988, when Lever and colleagues[36] published a clinical trial showing that patients treated with antibiotic plus steroid had greater improvement than those treated with steroid alone. White and others[37] proposed the existence of superantigens in 1989 to describe bacterial and viral proteins with the ability to stimulate large numbers of different T-cell clones and cytokine secretion. Further research has revealed that more than 50 per cent of *Staph aureus* strains carry several superantigens (SEA, SEB, TSST-1 and others). These antigens trigger inflammatory skin lesions typically seen in atopic dermatitis patients by stimulating the Th2 subset cytokine release. They stimulate Th2 T cells directly and act as a conventional allergen as well.[38] Infection with superantigen-carrying *Staph aureus* strains is one of the most important factors in the development of atopic dermatitis. Other bacteria, including *Streptococcus* species, and viruses have been shown to carry superantigens. Study of superantigens in the development of other allergic disorders such as asthma and allergic rhinitis may show similar results.

- **The 'Hygiene Hypothesis' of the late 1980s sought to link atopic disorders with the lack of early life infections**
- **This association is not new**
- **Early research into bacterial infections led to the discovery of the human immune system and the concept of allergy**

Summary

Allergy and infection have always been closely related and the study of one has often provided new insights into the pathobiology of the other. Early research into bacterial infections led to the discovery of the human immune system and the concept of allergy. An important relationship exists between parasite infections and the development of atopic disorders. Long-lived parasite infections may offer protection against atopic diseases by immunosuppression. They induce modulatory molecules that ameliorate host responses to enhance their survival. The precise linking elements are not known but both eosinophils and IgE globulins that occur so prominently in both disorders may be crucial to this relationship. Understanding the immunology of the host-parasite interaction and identifying the distinct parasite molecules with the immunomodulating effects may help to combat allergy more successfully.

The hygiene hypothesis re-emphasized the inverse relationship between infection and allergy. Helminth research has once again provided key insights into the possible immunological explanation. The initial Th1-Th2 dichotomy provided the earliest immunological explanation for the hypothesis but there are major discrepancies. Several researchers have forwarded alternative immunological concepts in an attempt to re-justify the original hygiene hypothesis.

Modified Th-2 responses seen in parasite infections may provide protective 'blocking IgG4 globulins' that inhibit allergic responses. Protective programming of the fetal immune system by exposure to early infections or other environmental factors may be the critical factor against later atopic conditions. The identification of superantigens in the development of atopic skin lesions provides further insight into this interesting relationship. Research may well show that allergy is an unfortunate by-product of an evolutionary mechanism developed to combat bacteria, parasites and other organisms. We have come around in a full circle. Allergy started with the study of infections and today we still look at infections for answers to allergic conditions. The exact link between allergy and infection may provide a means of effective and successful treatment of these two important human problems. Alternative approaches such as the use of *Mycobacterium vaccae*, Th1 adjuvants such as IL-12 or the use of immunostimulatory nucleotides (CpG) are examples of potential new therapies.

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