

Hypothesis: decreased use of pediatric aspirin has contributed to the increasing prevalence of childhood asthma

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Background: The prevalence of asthma, atopic eczema, and allergic rhinitis has increased over the last three decades in Western countries. Speculation on the causes of this trend have focused on changes in environmental factors. We hypothesize that the decreased use of aspirin in favor of acetaminophen, due to the association of aspirin with Reye's syndrome during febrile respiratory infections, may be contributing to these trends in the United States.

Data Sources: A detailed literature search was conducted utilizing Medline. Studies considered relevant and important involving both humans and animals in English language were used.

Hypothesis: In the United States, the documented prevalence of childhood asthma has increased since 1970, but the rate of this increase accelerated upward beginning in the early 1980s when the use of pediatric aspirin decreased. During the resolution of common respiratory viral infections, prostaglandin E₂ (PGE₂) is produced through the actions of cyclooxygenase-2 (COX-2). Aspirin, but not acetaminophen, inhibits COX-2 activity. As PGE₂ promotes TH2 and inhibits TH1 type cytokine generation, we hypothesize that the decreased use of aspirin may be a factor in facilitating allergic sensitization and asthma by augmenting the relative TH1/TH2 cytokine imbalance in genetically predisposed children.

Conclusion: We have presented an hypothesis based upon epidemiologic trends, known biologic effects of cytokines and PGE₂ on allergic sensitization, and a potentially relevant pharmacologic effect of aspirin to explain a component of the increasing prevalence of childhood asthma in the United States. We suggest this theory be examined further in animal models as well as in other countries where the prevalence of childhood asthma is increasing.

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INTRODUCTION

The prevalence of childhood allergic diseases, such as asthma, rhinitis, and atopic dermatitis has increased dramatically in Western societies over the last three decades.¹ It is doubtful that in less than two generations an evolutionary change in human genetics^{2,3} could have occurred to account for this trend. Research has therefore, focused on

Western environmental factors such as air pollution,⁴ indoor allergen^{5,6} and tobacco smoke exposure,⁷ diet,⁸⁻¹⁰ and changes in childhood exposures to infectious diseases.¹¹⁻¹³ We hypothesize that an unrecognized change in the care of children in modern Western societies, the decline in aspirin use, may be related to this increase in childhood allergic diseases and asthma due to the loss of aspirin's potential immunomodulatory properties and its influence on lymphocyte cytokine generation.

TH1 AND TH2 PATTERNS OF CYTOKINE EXPRESSION

Environmental factors present during infancy and early childhood influence

the development of immune responses to antigen.¹⁴ Recent interest has focused on the relative contribution of the two pathways of T helper cell cytokine expression: TH1 and TH2.¹⁵ Activation of the immune system by acute bacterial and viral infections stimulates pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) through activation of transcription factor NF κ B. A TH1 type lymphocyte response ensues with the initial generation of cytokines including IL-2, IL-12, and interferon γ (IFN- γ). TH1 cytokines contribute to cell-mediated immunity and delayed hypersensitivity reactions. In contrast, allergens and helminths elicit a TH2 type response with formation of IL-4, IL-5, IL-10, and IL-13. TH2 cytokines contribute primarily to allergic inflammation involving IgE antibody production and eosinophils. A feedback system balances these two types of responses: IFN- γ and IL-12 suppress TH2 responses, whereas IL-4 and IL-10 inhibit TH1 responses.

The balance, or imbalance, between TH1 cytokines and TH2 cytokines early in life may be critical to the eventual phenotypic expression of allergic disease. Any factor that modifies the cytokine milieu present during initial antigen exposures during infancy and childhood could influence the nature of subsequent immune responses and induce lifelong preferential TH2 (allergic) or TH1 (non-allergic) responses to various environmental stimuli. As early as the newborn period, this dichotomy in cytokine profiles and predisposition for allergic disease may exist. For example, a deficiency in IFN- γ production from umbilical cord blood lymphocytes in infants born to atopic

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parents appears to be a risk factor for the subsequent development of atopic disease.¹⁶ Early exposure to allergens may be a factor in TH1 versus TH2 development as season of birth¹⁷ or house dust mite allergen exposure in sufficient concentrations during early childhood increases the risk for developing allergic sensitization and asthma.⁵ Not all individuals, however, with this inherent ability to produce antigen-specific IgE antibodies develop allergic rhinitis or asthma. Other inflammatory stimuli encountered during the development of the immune system may be adjuncts to the consolidation and expression of a TH1 (non-allergic) or TH2 (allergic) cytokine profile.

INFECTIONS

It has also been proposed that exposure to infectious agents early in life may be important in the development of allergic disease. Until recently, viral infections were thought to enhance allergic sensitization¹⁸ and animal models support this theory.^{19,20} Recent data, however, have been interpreted to suggest that viral infections during childhood promote TH1 responses and may prevent the development of allergic disease.^{11,12} Comparing East to West Germany, the lower incidence of allergic disorders present among East German children has been related to daycare

attendance and a larger number of siblings, as both factors would seem to increase the risk for more frequent respiratory infections at an earlier age. The inverse relationship between the number of siblings and risk of atopy was similar in both countries despite a much larger percentage of East German children being in daycare with presumed greater exposure to infections.²¹ Strachan et al²² in a study of adult women, recently found that the inverse relationship between number of siblings and risk of atopy was present only in relation to the number of brothers, not simply the number of total siblings. The hypothesis that more frequent infections occurring in early childhood explains the decreased risk of atopy related to increased sibling size may therefore be incorrect. Other unknown immunologic factors, such as the maternal immunologic response to male and female fetuses and first versus subsequent pregnancies, may be important.

As for exposure to other infectious agents, Shirakawa and coworkers¹³ reported that positive delayed hypersensitivity skin test reactions to purified protein derivative (PPD) was a *negative* risk factor for the development of allergic diseases. The authors concluded that the development of an immune response to *Mycobacterium tu-*

berculosis was protective against the development of allergies. If this hypothesis is correct, it is conceivable that successful widespread vaccination programs (such as the near eradication of measles) or the more frequent use of antibiotics in Western societies have resulted in a limited natural exposure to viral and bacterial illnesses that previously promoted TH1 development and suppressed TH2 promotion of allergic disease. In regards to the study by Shirakawa, a conclusion that a negative PPD skin test was simply a reflection of previously established TH2 immune deviation was not considered. It is known that patients with atopic dermatitis have impaired cell-mediated immunity and decreased delayed hypersensitivity reactions to antigens as compared with non-atopic individuals.²³

ASTHMA, ASPIRIN, AND REYE'S SYNDROME

All previous hypotheses, ie, air pollution, indoor allergen exposure, tobacco smoke exposure, diet, and change in frequency and type of infections due to exposure, vaccinations, or use of antibiotics, either alone or in concert, may have contributed to the gradual increase in childhood asthma and allergic disease in Western societies. In the United States, the prevalence of childhood asthma increased 23% from 1970 to 1980.²⁴ From 1980 to 1986, a rapid increase in the number of American children with asthma occurred when the prevalence of childhood asthma increased nearly 40%^{24,25} (Fig 1). Indeed, in children aged 5 to 9 years born before 1983, the prevalence of asthma was approximately 10%; in children of the same age born after 1983, the prevalence increased to 20%.²⁶ Consequently, we propose that an unrecognized change in the "environment" of American children must have occurred at this time.

Paralleling the rapid rise in childhood asthma has been an unappreciated aspect of childhood respiratory infections: the swift change in supportive treatment of these illnesses by physicians and parents over the last two decades. In the United States, the near

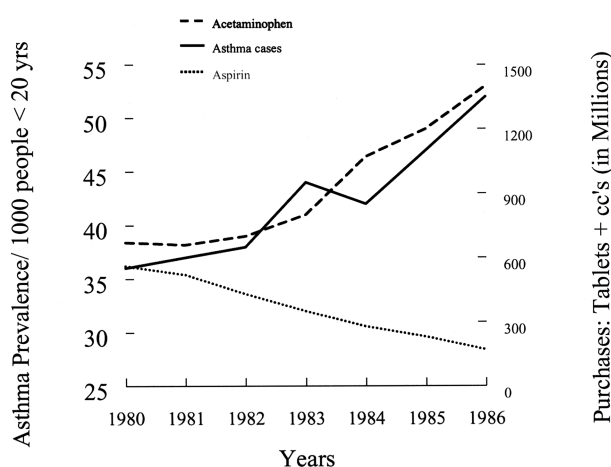


Figure 1. Prevalence of asthma in people under the age of 20 years and total drugstore purchases of pediatric aspirin (tablets) and acetaminophen (tablets + cc) in millions in the United States from 1980 to 1986.^{25,27}

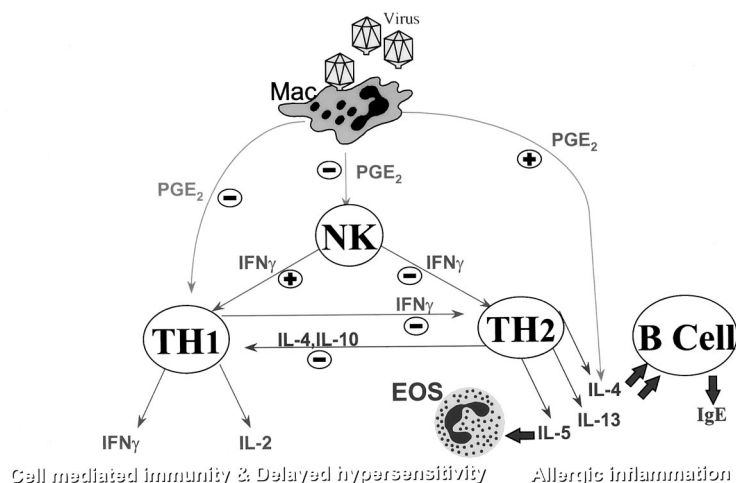


Figure 2. Schematic representation demonstrating the effects of virus induced macrophage mediators on the development of TH1/TH2 cytokines and immune responses. Mac = macrophage, NK = natural killer cell, Eos = eosinophils, (+) = stimulatory, and (-) = inhibitory.

complete discontinuation of the use of aspirin in infants and children occurred in the early 1980s due to an association with Reye's Syndrome after febrile respiratory infections²⁷ (Fig 1). Acetaminophen quickly became the pediatric antipyretic of choice in the United States as it had been in Australia and the United Kingdom for years.^{28,29} The consequences of this change in medication use during febrile respiratory infections in children and the potential immunomodulating effects of aspirin have not, heretofore, been considered as a possible cofactor in the increasing prevalence of allergic disease.

ASPIRIN, PGE₂, AND A TH2 CYTOKINE PROFILE

Respiratory viral infections are potent inducers of arachidonic acid products, particularly during the resolution phase of acute inflammation after the initial release of TH1 anti-viral cytokines.³⁰ Acute pro-inflammatory cytokines such as IL-1³¹ activate cyclooxygenase-2 (COX-2 or prostaglandin H-2

synthase). Prostaglandin E₂ (PGE₂) is produced which influences the balance between TH1 and TH2 cytokines³² (Fig 2). For example, prostaglandin E₂ inhibits IFN- γ and IL-2, but not IL-4, production from TH1 and TH2 lymphocytes, respectively.³³⁻³⁵ Furthermore, PGE₂ inhibits NK cells³⁶ and IL-12 production from macrophages and peripheral blood monocytes³⁷ which would further diminish IFN- γ generation. Prostaglandin E₂ can also, alone or synergistically with IL-4, promote isotype switching to favor IgE antibody production from B cells.³⁸ Interleukin-4, in addition to promotion of TH2 cytokines, inhibits COX-2 expression which leads to ultimate resolution of the acute inflammatory response.³⁹

High levels of PGE₂ produced during the resolution of childhood viral respiratory infections may promote a local TH2 cytokine environment in the respiratory tract. Concomitant allergen exposure and antigen presentation occurring in this TH2-predominant cy-

tokine milieu could enhance the development of allergen-specific IgE antibody and TH2 memory lymphocytes that home to the upper and lower airways. The actions of PGE₂ could also result in a further loss of IFN- γ 's antifibrotic effect in atopic children who already have a relative deficiency of this TH1 cytokine. This could permit increased airway remodeling and sub-epithelial fibrosis during resolution of inflammation induced by a lower respiratory tract viral infection.^{40,41}

Aspirin blocks the COX-2 pathway of arachidonic acid metabolism and inhibits PGE₂ production; acetaminophen does not.⁴² Given these properties of aspirin, we hypothesize that the substitution of acetaminophen for aspirin has led to an uninhibited production of PGE₂ during viral illnesses with a resultant enhancement of the expression of TH2 cytokines such as IL-4 which is required to inactivate COX-2 (Table 1). COX inhibitors, in vitro and in vivo, have been shown to produce immunomodulatory effects by promoting production of TH1 cytokines, IFN- γ and IL-2, and enhancing cell-mediated immune responses such as delayed hypersensitivity reactions.⁴³⁻⁴⁵ The use of aspirin during febrile illnesses, therefore, may play a pivotal role in down-regulating the expression of allergic disease in those children genetically predisposed to TH2 type immune responses. The substitution of acetaminophen for aspirin removed the modulatory activity on PGE₂ generation, resulted in a shift in the TH1:TH2 balance toward TH2, and created an environment favorable to the development of allergy and asthma.

CONCLUSION

A number of important interactions likely occur among environmental factors (air pollution; indoor allergen exposure; and tobacco smoke exposure), diet, and infections in infancy and early childhood to strongly influence the development of allergic diseases and asthma. Although it is unlikely that the elimination of pediatric aspirin use alone has been responsible for the increase in childhood allergic disease

Table 1. The Effect of Aspirin and Acetaminophen on PGE₂ Synthesis, Cytokine Production, and Development of Allergy and Asthma

	PGE ₂	INF- γ (TH1)	IL-4 (TH2)	Allergy/Asthma
Aspirin	↓	↑	↓	↓
Acetaminophen	↑	↓	↑	↑

in Western culture, it may be an unrecognized and important contributor to the increase in asthma prevalence. Indeed, in Western countries such as Australia and Great Britain, where the use of acetaminophen rather than aspirin was more common than in America prior to 1982, the prevalence of childhood asthma is greater than in the United States.^{24,28,29} The epidemiologic and immunologic relationships regarding aspirin use and childhood asthma and allergic diseases are intriguing, but at present unproven. We suggest that further investigation be directed toward this and other factors which continue to propagate the alarming trend in childhood asthma prevalence over the past three decades.

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