

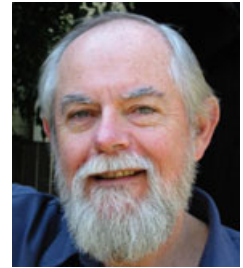
EDITORIAL

Prevention – what is the most promising approach?

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Immediately preceding the launch of *PAI*, the hygiene hypothesis was unleashed on an (at that stage) puzzled biomedical community by David Strachan in 1989 (1). Coincidentally, the groundbreaking review by Tim Mossman and Bob Coffman outlining the final synthesis of the Th1/Th2 model appeared in the same year (2), and the subsequent interplay between these seemingly unrelated sets of ideas was to prove pivotal in driving subsequent developments in the field of allergic diseases.

From a personal perspective, these two articles have provided the conceptual framework for much of my group's research activities in the ensuing 25 yr, and their impact was virtually immediate. In particular, we had shown in experimental models in the mid-1980s that natural resistance to aeroallergen sensitization was determined by a T-regulatory-cell-dependent mechanism operative in the airway mucosa, which was similar to the oral tolerance process in the GIT (3). Importantly, the option for development of protective immunologic tolerance was usually restricted to a window period around the time of initial exposures to environmental allergens, which in the human context serves to focus attention immediately on the first few years of life. Support for the importance of this life phase in allergy development was initially provided by pioneering studies from Bengt Bjorksten (4) and Tom Platts-Mills (5) tracking the post-natal development of IgE responses in children during the preschool years. Of particular interest to us was the cyclical nature of many of these early antibody responses (4), hinting at the underlying waxing and waning of the T-helper vs. T-regulatory responses that we hypothesized would ultimately determine the outcome of each new allergen encounter.

These ideas initially came together in the lead article published in the first issue of *PAI* in 1990 (6), introducing the general hypothesis that *gene × environment* interactions during infancy that influence the outcome of the mucosal immunologic tolerance process could determine lifelong responsiveness to environmental allergens. The central plank in this hypothesis was that 'risk' for failure of tolerance mechanisms leading to sensitization was accentuated during this early life period by the immaturity of many key immune functions, including

capacity to produce Th1-cytokines (6); based on the core concepts of the Th1/Th2 model (2), this would increase the likelihood that any early T-cell responses to allergen that escaped 'editing' by tolerance mechanisms would default down the Th2-memory pathway, leading to specific IgE production. Supporting evidence was soon provided by our T-cell cloning studies on infants, which demonstrated for the first time that delayed post-natal development of Th1/Th2 balance was a phenotypic marker of children at high genetic risk of allergy (7).

A follow-up review in *PAI* in 1995 (8) which focused on the role of environmental factors in susceptibility to allergic sensitization during infancy drew the first direct connections between the hygiene hypothesis, 'immune development', and susceptibility to allergic disease. This introduced the (then) radical concept that it was not so much microbial pathogens that mattered, but rather the totality of the microbial signals present in an individual's environment. In particular, we hypothesized that (i) the principal role of microbial stimuli in mediating protection against allergic sensitization in children was to accelerate normal post-natal maturation of immune functions and (ii) in addition to pathogens, a major source of the 'protective' signals emanating from the microbial environment was the *constituents of the normal gastrointestinal flora* (8). There is growing support for this notion (e.g., Ref. 9), and associations between post-natal colonization with microbial flora and risk for a range of diseases have become an area of intensive research.

It has also become clear in this context that pathogens truly represent a double-edged sword. Thus, while environmental exposure to some viral pathogens has been associated with increased resistance to allergic disease (e.g., Ref. 10), the converse is the case for many others. The notable example is the relationship between viruses and atopic asthma. In particular, severe respiratory viral infections, especially during infancy, are strongly associated with subsequent development of asthma (11–14) and also with triggering of exacerbations once asthma is established (11–13, 15). Emerging evidence also suggests a role for secondary bacterial infections in this context (12).

With respect to asthma initiation, these infections can function as independent risk factors; however, when they

occur against a background of sensitization to aeroallergens, the risk is markedly increased (15–17), implying underlying synergistic interactions between host inflammatory pathways triggered by these two different classes of antigen (11).

This same comorbidity is observed in children experiencing severe asthma exacerbations necessitating hospitalization (11–13). Our recent studies in these subjects (reviewed in Ref. 11) have identified some of the major interacting inflammatory mechanisms triggered during these events. One of particular relevance involves initial upregulation of expression of FcER1 on airway mucosal dendritic cells (DC) via stimulation of the receptor gamma chain by type 1 IFN released locally as part of the initial host antiviral response (18). A strong body of published data indicates that induction of FcER1 expression on DC in atopic dermatitis lesions results in marked enhancement of local Th2-associated inflammation via IgE-FcER1-facilitated allergen presentation to Th2 memory cells (19); comparable FcER1 upregulation on airway DC in virally infected atopic subjects concomitantly exposed to aeroallergen would likely have comparable consequences, introducing a strong Th2 cytokine signal into the local microenvironment; as well as being pro-inflammatory *per se*, this is likely to compromise viral clearance via immune deviation of Th1-polarized antiviral immunity (11). This mechanism also includes a systemic amplification loop, which operates during virus-associated exacerbations via translocation of a combination of type 1 IFN and Th2 cytokine signals to bone marrow, resulting in pre-arming of DC and monocyte precursors with FcER1 prior to their release into the blood; this may serve to further amplify IgE-FcER1-mediated inflammation at the infection site and may also contribute to the spread of atopic inflammation to other tissues via seeding of FcER1-bearing antigen-presenting cells (APC) into previously quiescent resident APC populations (an example of the 'atopic march' in Ref. 11).

Activation of this FcER1-associated pathway has also been demonstrated in sputum cell populations harvested from atopic children during viral-triggered asthma exacerbations (20). Moreover, interaction between the relevant antiviral and atopic pathways clearly occurs across the full spectrum of asthma disease severity, as evidenced by findings demonstrating the higher frequency and severity of symptomatic lower respiratory tract events accompanying winter viral infections in atopic vs. non-atopic asthmatic children (21). These episodes are frequently associated with subsequent decline in lung

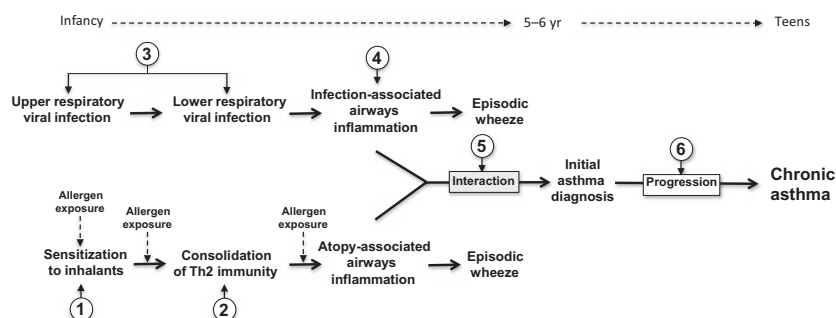
function (22), and their repeated recurrence is likely to provide a major drive toward asthma chronicity (11, 12).

These causal pathways are illustrated in Fig 1 and provide a blueprint for development and testing of primary and secondary prevention strategies applicable during childhood. The major factor limiting progress in this area is the availability of relevant therapeutic agents with a proven safety profile in young children. This will change rapidly over the next few years. However, a number of approaches are already testable, and a series in which our group and our collaborators are currently involved is summarized in Fig 1 and below:

1. *Preventing primary allergic sensitization.* We recently published the results of a pilot study which attempted to apply mucosal tolerance principles to boost resistance to primary allergic sensitization to inhalant allergens in high-risk children (23). This involved daily exposure of the oral mucosa to a mixture of allergens over 1 yr. The sample size was sufficient for safety analysis only, and in that respect, no evidence of significant adverse effects was obtained. Planning for a follow-up trial with larger sample size and modified allergen delivery protocol is in progress.

2. *Blocking consolidation of allergen-specific Th2 immunity post-sensitization.* Immune responses to environmental allergens maintain plasticity for many years after initial priming, and the evidence supporting the effectiveness of specific immunotherapy in atopic children is steadily accumulating. Of particular relevance is the PAT study targeting rhinitic children sensitized to birch pollen, demonstrating immunotherapy-associated protection against subsequent asthma onset (24). The underlying mechanism may be explicable in the context of the model proposed recently for the 'allergic march' in which Th2-associated signals from inflammatory sites exemplified by the nasal mucosa can influence FcER1 expression on antigen-presenting myeloid cells (APC) in secondary tissues, via effects on precursor populations in bone marrow (11). There is an urgent need for larger preventive trials of this nature targeting sensitized children.

3, 4. *Prevention and/or attenuation of the inflammatory sequelae of infant lower respiratory infections.* In the absence of pathogen-specific vaccines targeting the respiratory viruses responsible for the bulk of infant/preschooler infections, a testable option is the class of bacterial-derived orally-delivered immunostimulants that boost systemic mucosal immune defenses through effects mediated via gut-associated lymphoid



tissues [reviewed (11)]. Exemplary of these is OM-85 which has been used successfully in RCTs to reduce the frequency/severity of wheezing events in infants (25); boosting of mucosal-homing T-regulatory cell activity appears to be one of the mechanisms of action of this agent, but other pathways may also be involved (11). We are currently testing this preparation in Australia in infants at high risk of atopy/asthma in government-sponsored trials, initially targeting infections during the first 2 yr of life.

5. *Blocking interactions between atopic and antiviral pathways in children with intermittent wheeze.* As noted earlier (11), the interaction between these pathways is mediated via specific IgE bound to FcER1 on myeloid APCs. In light of US findings that treatment of asthmatic children continuously with Xolair markedly reduced the frequency of exacerbations especially during the autumn viral season (26), it appears logical to also test this agent or equivalent in atopic wheezers prior to asthma diagnosis. However, it should be noted that safety data are currently only available down to age 6 yr.

6. *Blocking progression from intermittent to persistent/chronic atopic asthma in childhood.* As noted (11, 12), it appears likely that these same interacting pathways are major contributors to progression in atopic children beyond initial asthma diagnosis toward asthma persistence/chronicity. We are accordingly currently testing the proposition that prophylactically treating high-risk atopic asthmatic school children with a history of prior virus-associated exacerbations on a 'winter only' basis (i.e., over the local virus season) will reduce the frequency of virus-induced exacerbations and associated loss of asthma control. A similar approach is planned for the immunostimulant OM-85 for the winter of 2014.

The approaches detailed above are designed to obtain proof of concept that (if successful) would justify larger and much longer trials targeting asthma prevention in different age groups. It has taken the 25 yr since *PAI* was launched to reach this point; we are increasingly hopeful that we won't need to wait until the 50th anniversary before real progress in asthma prevention is achieved.

References

- Strachan DP. Hay fever, hygiene, and household size. *Br Med J* 1989; **299**: 1259–60.
- Mosmann TR, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol* 1989; **7**: 145–73.
- Holt PG, Sedgwick JD. Suppression of IgE responses following antigen inhalation: a natural homeostatic mechanism which limits sensitization to aeroallergens. *Immunol Today* 1987; **8**: 14–5.
- Hatlevig G, Kjellman B, Björkstén B. Clinical symptoms and IgE responses to common proteins and inhalants in the first 7 years of life. *Clin Allergy* 1987; **17**: 571–8.
- Rowntree S, Cogswell JJ, Platts-Mills TAE, Mitchell EB. Development of IgE and IgG antibodies to food and inhalant allergens in children at risk of allergic disease. *Arch Dis Child* 1985; **60**: 727–35.
- Holt PG, McMenamin C, Nelson D. Primary sensitisation to inhaled allergens during infancy. *Pediatr Allergy Immunol* 1990; **1**: 3–13.
- Holt PG, Clough JB, Holt BJ, et al. Genetic 'risk' for atopy is associated with delayed postnatal maturation of T-cell competence. *Clin Exp Allergy* 1992; **22**: 1093–9.
- Holt PG. Environmental factors and primary T-cell sensitization to inhalant allergens in infancy: reappraisal of the role of infections and air pollution [Review]. *Pediatr Allergy Immunol* 1995; **6**: 1–10.
- Björkstén B. Impact of gastrointestinal flora on systemic diseases. *J Pediatr Gastroenterol Nutr* 2008; **46**(Suppl. 1): E12–3.
- Matricardi PM, Rosmini F, Riondino S, et al. Exposure of foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000; **320**: 412–7.
- Holt PG, Sly PD. Viral Infections and atopy in asthma pathogenesis: new rationales for asthma prevention and treatment. *Nat Med* 2012; **18**: 726–35.
- Holt PG, Strickland DH, Hales BJ, Sly PD. Defective "immune surveillance" of respiratory mucosal surfaces: a primary causal factor in asthma onset and progression. *Chest* 2013a; doi: 10.1378/chest.13-1341, in press.
- Sly PD, Boner AL, Björkstén B, et al. Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008; **372**: 1100–6.
- Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007; **370**: 758–64.
- Busse WW, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet* 2010; **376**: 826–34.
- Holt P, Rowe J, Kusel M, et al. Toward improved prediction of risk for atopy and asthma amongst preschoolers: a prospective cohort study. *J Allergy Clin Immunol* 2010; **125**: 643–51.
- Oddy WH, de Klerk NH, Sly PD, Holt PG. The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. *Eur Respir J* 2002; **19**: 899–905.
- Subrata LS, Bizzintino J, Mamessier E, et al. Interactions between innate antiviral and atopic immunoinflammatory pathways precipitate and sustain asthma exacerbations in Children. *J Immunol* 2009; **183**: 2793–800.
- Novak N, Kraft S, Bieber T. Unraveling the mission of FcεRI on antigen-presenting cells. *J Allergy Clin Immunol* 2003; **111**: 38–44.
- Bosco A, Ehteshami S, Panyala S, Martinez FD. Interferon regulatory factor 7 is a major hub connecting interferon-mediated responses in virus-induced asthma exacerbations in vivo. *J Allergy Clin Immunol* 2012; **129**: 88–94.
- Olenec JP, Kim WK, Lee WM, et al. Weekly monitoring of children with asthma for infections and illness during common cold seasons. *J Allergy Clin Immunol* 2010; **125**: 1001–6 e1.
- O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009; **179**: 19–24.
- Holt PG, Sly PD, Sampson HA, et al. Prophylactic use of sublingual allergen immunotherapy in high risk children: a pilot study. *J Allergy Clin Immunol* 2013b; **132**: 991–3.
- Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; **62**: 943–8.
- Razi CH, Harmanci K, Abaci A, et al. The immunostimulant OM-85 BV prevents wheezing attacks in preschool children. *J Allergy Clin Immunol* 2010; **126**: 763–9.
- Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011; **364**: 1005–15.