Commentary

The hygiene hypothesis in the development of atopy and asthma—still a matter of controversy?

L.C. VON HERTZEN

From the The Finnish Lung Health Association, Helsinki, Finland

Introduction

The remarkable increase in asthma and atopy prevalences during the last few decades in Western societies cannot be explained by changes in genetic factors or by improvements in diagnostic procedures only. Environmental factors, particularly those associated with a Westernized lifestyle, are considered to be involved in this increase. In the late 1980s, Strachan found that repeated infections in early life may prevent the development of hay fever. He further suggested that the most significant cause of the increase in atopic diseases in Western countries is the decreased exposure to cross-infections among younger siblings as the result of decreased family size. Concomitantly, Romagnani suggested that the rising prevalence of atopy could be related to the strong reduction in childhood infections, particularly tuberculous infections that stimulate the production of cytokines antagonistic to Th2 cell differentiation. This ‘hygiene hypothesis’ has now gained wide acceptance as the most plausible explanation of the increase in atopic diseases. Several recent studies have provided further evidence that certain invasive infections, such as Mycobacterium tuberculosis, hepatitis A and measles infection in childhood may prevent the development of atopy and atopic diseases in later life. By contrast, no similar effect has been found for vaccination. Neither measles vaccination nor BCG vaccination in children with atopic heredity has shown any significant effect on the subsequent development of atopy. It appears that only certain natural infections in childhood that are of sufficient intensity might be able to decrease susceptibility to atopy.

Infections that may have an immunomodulatory effect

It is uncertain which infections may have an immunomodulatory role in early life, but micro-organisms that elicit a vigorous cell-mediated immunity (a Th1-type response), particularly intracellular bacteria and viruses, would be the most logical candidates. It is probably fundamental that the infection be invasive, protracted or repeated. Data obtained from human studies thus far have suggested a role for the intracellular bacterium, M. tuberculosis, and for the two single-stranded RNA viruses, measles and hepatitis A, which generally elicit a lifelong immunity. Short-lived immunity is often associated with localized mucosal infections (e.g. common cold infections), whereas long-term protective immunity is a feature of many systemic infections (e.g. measles, polio and mumps). Local mucosal infections, even though occurring recurrently, seem not to play a significant role here. However, there is some evid-
ence to suggest that microbes with immunomodulating properties may not be restricted to pathogens alone. Colonizing or persisting microbes could also be important, particularly those involved in the microflora of the gut, affecting systemic immunity via the gut-associated lymphoid tissue.\textsuperscript{12,13} The wide usage of antibiotics in children during the last decades is assumed to have had an impact also on this balance of gut-associated immunity.\textsuperscript{12}

**Possible mechanisms involved in infection-induced immunomodulation**

The hygiene hypothesis is based on the widely accepted concept of the divergence of differentiated murine and human T cells into two major effector cell subsets, Th1 and Th2 cells, that are largely mutually inhibitory and reciprocally regulated (reviewed in references 14 and 15). Although the T-cell effector mechanisms have proved to be much more complex,\textsuperscript{16} this concept has been applicable and relevant in many infectious, allergic and autoimmune diseases.\textsuperscript{17} It is assumed that environmental factors, particularly the lack or presence of systemic infections in childhood, play a significant role in determining the expression of dominant T-cell phenotype in children who are genetically predisposed.\textsuperscript{18} Certain invasive or repeated infections during early life may selectively enhance the development of Th1 cells, thus inhibiting the proliferation of Th2 cells and the development of allergic sensitization in genetically predisposed children.\textsuperscript{19} Children mounting strong Th1 responses without a family history of atopy may not develop atopic diseases even when living in an environment where the exposure to infections is low.\textsuperscript{20}

The innate immune system, comprising macrophages, natural killer (NK) cells and neutrophils, is considered to be of crucial importance in early immune defence against foreign antigens and in committing the adaptive immune system.\textsuperscript{21} Microorganisms, particularly intracellular pathogens, induce macrophages to vigorous interleukin (IL)–12 production, which in turn induce NK cells and later Th1 cells to produce IFN-\(\gamma\).\textsuperscript{22} IL–12 is the single major factor required for the proper differentiation of Th1 cells, and thus the ability of a micro-organism to trigger production of this cytokine is a key determinant in the initiation of a successful immune response. IL–12, produced mainly by macrophages and dendritic cells during the early phases of an infection, and IFN-\(\gamma\), produced by T and NK cells, provide an environment in which antigen specific CD4+ and CD8+ T cells are preferentially induced to differentiate into Th1 cells with even higher IFN-\(\gamma\) production.\textsuperscript{23} It is reasonable to hypothesize that if vigorous IL–12 production by macrophages or dendritic cells does not take place during the early phases of the first systemic infections in childhood, a predominance of Th2 cells may develop in genetically predisposed children, leading to atopy.

Studies on murine listerosis have shown that actively replicating bacteria are required for macrophage activation \textit{in vivo}, whereas non-viable or replication-incompetent bacteria or bacterial products have been found to be unable to influence the ability of macrophages to produce IL–12.\textsuperscript{24} Vaccines based solely on attenuated bacteria or viruses unable to replicate may therefore have only marginal, if any, Th1/Th2 modulating effect. By contrast, IL–12 used as a vaccine adjuvant has been shown to be able to shift the T-cell differentiation towards the Th1 phenotype in mice.\textsuperscript{25} It remains to be proven whether IL–12 as a vaccine adjuvant may have a similar beneficial effect in humans genetically prone to develop a Th2 rather than a Th1 response.

**Genetic predisposition**

The remarkable influence of the genetic make-up in successfully resolving infections has been shown in numerous animal studies and also in man.\textsuperscript{26–28} Hereditary factors undoubtedly play an important role in determining the susceptibility to atopy and asthma. Different mice strains exhibit significant differences in IL–12 production, particularly in antigen-driven processes.\textsuperscript{29} The effect of the genetic background on the development of biased cytokine profiles in primed CD4+ T cells is at least in part due to differential production of IL–12.\textsuperscript{29} This Th2 profile appears to occur prenatally via transplacental transfer, particularly during the last trimester.\textsuperscript{31} This Th2 priming may be strongest in infants with family history of atopy, suggesting the involvement of genetic alterations in mechanisms that control IL–4 production in atopy.\textsuperscript{32} Indeed, atopic asthmatic children have been found to produce lower levels of IFN-\(\gamma\) as compared to healthy children. This lower IFN-\(\gamma\) production has been shown to be significantly related to impaired lung function, suggesting that depressed production of IFN-\(\gamma\) may be an important factor in the pathophysiology of atopic asthma.\textsuperscript{32}
There are also nongenetic factors, such as maternal smoking, that could pre- or postnatally influence the risk of atopy. Cigarette smoking increases the production of IL–4 by peripheral blood mononuclear cells (PBMC) resulting in increased serum IgE levels of both the mother and fetus.\textsuperscript{33,34} However, the association between maternal smoking and the subsequent development of atopy in the offspring remains controversial.\textsuperscript{35} Similarly, the current evidence provides conflicting and scanty support for such factors as changing indoor allergen exposure, chemical air pollution, infant feeding or dietary pattern in the etiology of atopic diseases.\textsuperscript{12}

**Reversal of Th1/Th2 balance**

Alteration of established T-cell clones has been considered to be difficult, although the activation stage of T cells appears to play a critical role in their ability to respond to IL–12\textsuperscript{29} and in the subsequent alteration of the Th1/Th2 balance. Studies on murine leishmaniasis and intestinal parasitic infections have shown that once Th2 cells become established, Th2 cytokine synthesis cannot be inhibited by IL–12, and IL–12 appears to have only a limited role in downregulating Th2 cytokine synthesis in secondary immune responses.\textsuperscript{29} However, the addition of IL–12 inhibits IL–4 and IL–10 synthesis in resting memory CD4\textsuperscript{+} T cells. IL–12 can alter the cytokine profiles of memory CD4\textsuperscript{+} T cells by increasing IFN-\(\gamma\) and inhibiting IL–4 and IL–10 synthesis. Activated memory T cells do not respond to IL–12.\textsuperscript{29} Moreover, it appears that restimulation increases the degree of T cell polarization, and that Th1 and Th2 cell populations generated by chronic antigenic stimulation in the presence of polarizing cytokine are irreversible. Repeated stimulation result in a higher degree of homogeneity and renders the cell population more resistant to change. However, Th1 cell clones show some plasticity towards Th2 cells in the presence of IL–4, even after repeated antigenic stimulation, whereas Th2 cells in the presence of IL–12 after repeated antigenic stimulation appears to be irreversible.\textsuperscript{36} This implies that it may be more possible to dampen or revert inflammatory Th1 pathologies than atopic Th2-dominated diseases.\textsuperscript{36}

**Critical time period**

The time period that is critical for the reversal of the Th1/Th2 balance is not exactly known. The maturation of the immune system has been proposed to continue up to 5–7 years of age,\textsuperscript{37} and by that time repeated and/or systemic infections may be of importance. Data from animal studies indicate that the immune system of newborns is intrinsically polarized to a Th2 pattern at birth in virtually all subjects, and this polarization, dominated by the high-level production of the Th1-inhibitory cytokine IL–10, is obviously maintained for a significant period during infancy. This Th2 response is reversed by the emergence of a later Th1 type response dominated by IFN-\(\gamma\) in non-atopic subjects.\textsuperscript{33} Recent work in humans suggests that by a median age of 5 years, children can be divided into non-atopics or atopics on the basis of skin-prick-test positivity to common aeroallergens. Those children with positive skin prick test showed a mixed Th0 type response, whereas those who were skin-prick-test negative demonstrated IFN-\(\gamma\) responses in the absence of Th2 cytokines.\textsuperscript{38} High-level production of Th2 cytokines by allergen-specific T cells, and conversely a deficient IFN-\(\gamma\) production, may be found already in cord blood.\textsuperscript{39,40} and this biased prenatal cytokine balance is expected to constitute a major risk factor for the subsequent development of atopy.\textsuperscript{31}

Although most studies have emphasized the importance of early life in the programming of the appropriate T-cell response and memory, alterations in T-cell responses may occur even in adulthood. A study of immigrants in Sweden showed that the spectrum of atopy in the immigrants became gradually more similar to that found in Swedish patients. Within a few years the immunological status of immigrants adapted to the new environment, emphasizing the importance of environmental factors in the manifestation of atopic diseases.\textsuperscript{41} The reduction of exposure to infections even in adulthood could thus induce atopic responses in genetically susceptible individuals.\textsuperscript{40} Further, the opposite phenomenon, a remission from atopic disease, although probably only temporarily, has been found in individuals after various infectious diseases.\textsuperscript{42}

**Conclusions**

An increasing body of evidence supports the concept that certain systemic infections in early life may reverse the Th response type by upregulating the Th1 type and depressing the Th2 type response, and thus highly reduce the probability of atopy in later life in children genetically predisposed to atopy and asthma. Inadequate levels of IL–12, the key cytokine in the early induction of an appropriate Th1-type response in intracellular infections, appears to play a fundamental role in the polarization of the response to a biased Th2 type in subjects prone to atopy. Recent data suggest a role for M. tuberculosis, measles and hepatitis A virus infections at an early age in preventing the subsequent development of atopy. It is logical to assume that several other microorganisms that are known to elicit a vigorous Th1
response may also affect the Th1/Th2 balance in early life. However, the hygiene hypothesis has not yet proven to be completely consistent, and it is possible there are factors not yet identified that may also be involved. Whether the unfavourable trends in asthma and atopy prevalences can be reversed with immuno-modulatory interventions remains to be seen.

References


