Wheeze is more common in infants and young children than at any other age. The reasons for this are still unclear, but various risk factors have been recognized. The most important of these is maternal smoking during pregnancy (1), but other factors have been described including inhaled tobacco smoke (2), reduced lung function at birth (3, 4), birth order, ethnic background, gender (5) and genetics.

Identifying risk factors for wheeze has provided little insight into mechanisms by which these factors affect the airway. This is particularly the case for maternal smoking during pregnancy. Earlier data suggested that the deleterious effect is via airway structure and function and indeed maternal smoking has been associated with reduced airway function as measured soon after birth (3) as well as increased thickness of airway smooth muscle in offspring dying of sudden infant death syndrome (6). However, more recent evidence points to a potentially more important effect of maternal smoking during pregnancy on the developing immune system. In 60 newborns with smoking mothers compared with 62 newborns with non-smoking mothers, cord blood mononuclear cell (CBMC) responses to toll-like receptor (TLR) ligands were attenuated for tumour necrosis factor α, IL-6 and IL-10 (7). These TLR responses were unrelated to maternal atopy. Hence, one of the potential mechanisms by which in utero exposure affects future wheeze susceptibility is via an effect on the innate immune system. This defect could be important in reducing natural immunity to early respiratory viral infections.

Ability to counter early acute respiratory viral infections may also be impaired via effects of in utero environmental tobacco smoke (ETS) exposure on the T-helper (Th) lymphocytes. If the responses of peripheral blood mononuclear cells (PBMC) from infants and young children with at least one smoking parent are compared with those from infants not exposed to ETS, little difference in PBMC responses would be noted between these two groups, as was the case in a recent study in which response to antigens was assessed as the response to vaccine antigens (8). However, if the groups are further stratified by alleles present in variations in several Th2-related genes, the pro-Th2 alleles in these genes have been shown to be related to reduced specific antibody production and reduced PBMC responses in infants exposed to either maternal or paternal ETS (8). These effects were noted for polymorphisms in the genes for interleukin-4 (IL-4), IL-4 receptor (IL-4R) and IL-13. These results were unexpected, in that ETS exposure affects Th1 immunity but does so via variations in Th2 genes, but the findings open the way to further investigations to follow these leads.

Further evidence that wheeze in early life may come from a relative impairment in defenses against respiratory viruses comes from a study in Dutch children (9, 10). In this study, specific antibody production against pneumococcal vaccine antigens was evaluated with respect to a range of Th1 and Th2 genotypes. Reduced specific IgG to all seven pneumococcal antigens was noted for the pro-Th2 allele of CD14 C-159T (10) and also for the pro-Th2 alleles of IL-4, IL-4R and IL-13. These results were unexpected, in that ETS exposure affects Th1 immunity but does so via variations in Th2 genes, but the findings open the way to further investigations to follow these leads.

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Thus, several lines of evidence now point to a relative impairment in the responses of the immune system in early life in infants who are likely to wheeze. To date, this has been noted in infants exposed to tobacco smoke and in those with pro-Th2 genotypes, with evidence that links these factors. Whether these impairments in immune function are related to increased wheeze via an inability to resist respiratory viral infections has not been directly ascertained to date, although the hypothesis that they are is well worth testing.

Infants destined to become atopic and asthmatic demonstrate a delay in maturation of the immune system in early life. The fetal intra-uterine environment is skewed towards Th2 responses (11) and
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CBMC demonstrate this (12) (13). At birth, T-cell responses are already different between infants (14) and the levels of Th2 related cytokines produced by CBMC are reduced in infants of atopic mothers (15). The degree of delay in maturation of immune system responses may be different in future atopics (11). In accord with this, cord blood levels of both Th1 and Th2 cytokines were reduced in infants who later developed asthma (16). These deviations in immune system function could contribute to an increased susceptibility to respiratory viral infection in early life. The time course of the resolution of these changes has been suggested by studies of vaccine responses. These studies are ideal to evaluate responses to antigens, as the exposure to antigen in vaccine studies is precise and tightly controlled with respect to both dose and timing. The delay in interferon gamma (IFN-γ) production was noted to accompany the reduction Th2 cytokine responses to specific vaccine allergens (17). The IFN-γ responses recovered by 12 to 18 months of age and at this age, subjects with a parental history of atopy also began to exhibit exaggerated Th2 responses (18). This time course coincides with the high prevalence of virus-induced wheeze at this stage in life.

Recent studies have pointed towards the very high prevalence of viral respiratory infections in early life as the main cause of wheezing episodes. In a community study, the majority of infants had between two and five episodes of acute respiratory infection in the first year of life and of these, one third were lower respiratory infections and approximately one third of these were associated with wheeze (19). Nearly half the respiratory episodes were associated with rhinovirus, with only around 10% associated with respiratory syncytial virus. This study establishes rhinovirus as the most common cause of wheezing in infants and therefore current data shows that rhinovirus is the most common cause of wheezing throughout life (20) (21) (22) (23) (24). Defects in Th1 responses have been demonstrated in older asthmatic subjects (23, 25, 26) (27) (28) and these are likely to be causally linked to the increased susceptibility of asthmatics to viral respiratory infections (29) (26).

The challenge in future studies of wheeze in early life is to more precisely determine the mechanisms by which the immune system fails to protect infants from viral respiratory infections. This is particularly important for understanding how and why impairment in Th1 responses accompanies the altered Th2 function observed in atopics. Understanding how maternal smoking affects early immune function in infants is also important and may provide insight into where the most critical problems lie.

REFERENCES:
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