

Diet, infection and wheezy illness: lessons from adults

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An increase in asthma and atopic disease has been recorded in many countries where society has become more prosperous. We have investigated two possible explanations: a reduction in childhood infections and a change in diet. In a cohort of people followed up since 1964, originally selected as a random sample of primary school children, we have investigated the relevance of family size and the common childhood infectious diseases to development of eczema, hay fever and asthma. Although membership of a large family reduced risks of hay fever and eczema (but not asthma), this was not explained by the infections the child had suffered. Indeed, the more infections the child had had, the greater the likelihood of asthma, although measles gave a modest measure of protection. We have investigated dietary factors in two separate studies. In the first, we have shown the risks of bronchial hyper-reactivity are increased seven-fold among those with the lowest intake of vitamin C, while the lowest intake of saturated fats gave a 10-fold protection. In the second, we have shown that the risk of adult-onset wheezy illness is increased five-fold by the lowest intake of vitamin E and doubled by the lowest intake of vitamin C. These results were supported by direct measurements of the vitamins and triglycerides in plasma. We have proposed that changes in the diet of pregnant women may have reflected those observed in the population as a whole and that these may have resulted in the birth of cohorts of children predisposed to atopy and asthma. The direct test of this is to study the diet and nutritional status of a large cohort of pregnant women and to follow their offspring forward. This is our current research.

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The increase in asthma and atopic disease that occurs when society becomes more sophisticated and prosperous has been observed world-wide, and constitutes one of the great enigmas of modern medicine. It is of considerable public health and economic importance and, since it has accompanied social change, it is more likely that a solution to the problem will come from a public health approach than from the discovery of new drugs. In looking for an explanation, therefore, a primary environmental cause requires to be sought, rather than a secondary, mechanistic, explanation in terms of disordered function of the airways and their cells.

It is logical to suppose that any change in prevalence of disease over as short a period as two

or three decades is likely to be due either to changes in lifestyle factors affecting the whole population or to very dramatic changes in the toxicity of the environment. Any hypothetical causes should have a reasonable chance of explaining not only the serial changes observed in countries such as the UK and New Zealand, but also the differences between groups of people in the same and in different countries. Here, urban-rural and East-West European differences also provide a challenge. What factors in society have changed sufficiently to provide a hypothetical explanation?

There is little evidence that there has been an increase generally in exposure to the common allergens, mites, grass pollen and cat protein, to

which children become sensitized, and a considerable rise in these would have been necessary to have led to a doubling in the prevalence of asthma. Indeed, there is evidence that hay fever has increased in spite of no rise in grass pollen levels (1). Similarly, both urban air pollution and cigarette smoking by young adults have decreased, making it very unlikely that either of these is a factor in the rise in allergic disease. Other possible causes must therefore be sought, and of these the most plausible are changes in the incidence of childhood infections and changes in the diet of the population.

The concept that a reduction in childhood infections may have led to a rise in atopic disease arose from the observations of an association between family size and atopy, members of large sibships having lower risks of atopy (2). An obvious, though not necessarily correct, explanation is that infections spread around larger families and so children in such families are more at risk of catching them. It has therefore been argued that certain infections might switch the child's immune defences from a predominantly atopic, T helper (Th)-2 lymphocyte-mediated response to an anti-infection Th-1 response (3). There is good evidence that increasing prosperity of society is associated with a reduction in the common infections and infestations of childhood. Yet such an antigenic challenge may be necessary in biological terms for the full development of an immune system required to deal with such infections, and if this challenge is sub-optimal, the individual may retain an earlier immune responsiveness leading to atopy. Several epidemiological studies have addressed this hypothesis. It has been shown that children who had suffered measles in West Africa were less likely to be atopic than those who did not get the disease (4). Similarly, children who had evidence of tuberculous sensitization in Japan were at reduced risk of atopy, as were Italian military recruits who had serological evidence of past hepatitis A infection (5, 6). In none of these cases, however, did the infection appear to have protected against asthma.

Our own studies have shown, in a cohort of children examined first in 1964, that the common infectious diseases of childhood appear collectively to have *increased* slightly the risks of asthma (7). Only measles appears to have had a modest protective effect. Nevertheless, this cohort of children showed the family size effect with respect to both hay fever and eczema, members of large sibships showing a reduced risk of both conditions. It appears from the literature that there is a true effect of family size but that it is at best only

partly explained by infections, leaving an intriguing question to be answered. What could it be due to? We speculate that the immune or nutritional function of the placenta may change with succeeding pregnancies, altering the immune development of the neonate.

This brings us to the question of nutrition in determining the risk of atopy and asthma. This thought first occurred as a result of noticing how consumption of fresh fruit and vegetables had declined in Britain as atopic disease had risen (8). There was already published evidence that antioxidants afforded some protection against airflow obstruction. We proposed that a population shift in intake of antioxidants, reflected in the diet of pregnant women, might have been sufficient to explain the rise in asthma if children were born with, on average, poorer defences against inhaled allergens. This suggestion that diet might be influential has attracted some attention, and a further hypothesis has been based on it, suggesting that changes in the fatty acid rather than antioxidant content of the diet might have been responsible for the increase in asthma (9).

These two hypotheses are complementary and deserve serious consideration. As societies become more prosperous, diet changes towards one in which the original source of food on the plate is less obvious and the food we eat is further removed in time from its harvest. There is evidence that intake of fresh food of all sorts has declined in Britain and it is likely that there has been a shift from ω -3 to ω -6, and an increased proportion of hydrogenated, *trans*, fatty acids in our diet (10). There are theoretical reasons, discussed below, to suppose that such shifts across a pregnant population could increase the prevalence of atopy and asthma in the offspring. There is also some evidence that those eating a diet poor in antioxidants and high in fats are at increased risk of adult onset wheeze and of having hyper-reactive airways.

We have reported two studies investigating this issue. In the first we investigated the diet of individuals identified in a cross-sectional rural population study, comparing those with hyper-reactivity and those without, adjusting for age and smoking habit (11). The lowest tertile of intake of vitamin C was associated with a seven-fold increase in risk of having increased reactivity. In contrast, the lowest tertile of intake of saturated fats reduced the risk almost 10-fold. In the second study we examined the diets of individuals from a longitudinal cohort followed up since the 1960s, and compared those who had developed adult-onset wheezy illness with those who had not (12). The risks of wheeze were increased almost five-

fold in those with the lowest tertile of intake of vitamin E and doubled in relation to low vitamin C intake. These results were supported by measurement of plasma vitamin C and vitamin E corrected for triglycerides, the lowest concentrations of which again related to increased risk of wheeze. A low blood triglyceride level was, in contrast, a significant protective factor. It was noteworthy in this study that, when the subjects were separated by social class, these findings were only present in the manual group. In a third, as yet unpublished, study we have shown that a diet low in vegetables and/or vitamin E and calcium increased the risk of asthmatic symptoms in Saudi Arabian schoolchildren more than twofold, after taking account of area of residence (urban/rural), atopy, family history, parental smoking, and other possible confounding factors.

If dietary factors influence the development of asthma, they must be implicated in the pathogenesis of the bronchial mucosal inflammation that is characteristic of the condition. The immunopathogenesis of asthma has been clarified by the recognition that T-helper (Th) cell subsets play a pivotal role and that Th cells differentiate into two major phenotypes (Th-1 and Th-2) characterized by their cytokine release (13, 14). Studies of Th cells indicate that atopic asthma is associated with a bias towards the Th-2 phenotype (15) and secretion of the cytokines, interleukin (IL)-4 and IL-5, which influence IgE secretion and eosinophil chemotaxis. A small number of reports of *in vitro* studies provide tantalising data suggesting that antioxidants and polyunsaturated fatty acids can bias Th-cell differentiation towards the Th-2 phenotype.

The glutathione/glutathione peroxidase metabolic pathway plays an important role in removing intra-cellular hydrogen peroxide and the damaging lipid and phospholipid hydroperoxides generated by free radicals. N-acetyl-L-cysteine is an antioxidant precursor of glutathione, and both have been shown *in vitro* to decrease in a dose-dependent manner the secretion of IL-4 by human Th-cell clones and the secretion of IgE by human peripheral blood mononuclear cells co-cultured with IL-4. The absence of an effect on interferon- γ suggests that the antioxidants N-acetyl-L-cysteine and glutathione promote the Th-1 phenotype; this raises the possibility that deficiencies in glutathione may be associated with the Th-2 phenotype (16). A key component of glutathione peroxidase is selenium, a low dietary intake of which has been reported in patients with asthma (17, 18). Recent UK studies have also indicated that the consumption of selenium has nearly halved in the last 20 years to a level consistent with

widespread sub-clinical selenium deficiency (19, 20).

The antioxidant vitamins A and E have been shown to influence Th-cell differentiation in murine models. Retinoic acid and vitamin A inhibit *in vitro* IL-4 dependent IgE production by lipopolysaccharide (LPS) stimulated murine spleen cells, suggesting a possible immunomodulatory role for this vitamin (21). The possible immunomodulatory effects of vitamin E have been demonstrated in the murine model of AIDS (22). In this model, retroviral infection is associated with a marked reduction in serum and hepatic vitamin E levels. In response to mitogens and LPS, the splenocytes release low levels of interferon- γ and high levels of IL-4. Normalization of serum and hepatic vitamin E levels by dietary supplementation is associated with increased secretion of interferon- γ and reduced secretion of IL-4.

As mentioned above, the roles of antioxidants and polyunsaturated fatty acids (PUFA) in the aetiology of asthma are probably complementary. At the metabolic level, complex pathways involving vitamins C and E protect fatty acids incorporated in phospholipids from oxidative damage by free radicals. The importance of considering both antioxidants and PUFA in conjunction has been demonstrated in a dietary supplementation study (23). The T-cells from monkeys fed a diet supplemented with fish-derived ω -3 PUFA demonstrated increased proliferation and secretion of IL-2 in response to mitogens, whereas the T-cells from monkeys fed plant-derived ω -3 PUFA demonstrated no such change. This difference proved to be the consequence of a dietary deficiency in tocopherol in the diet supplemented with plant-derived ω -3 PUFA, a deficiency manifest by oxidative changes in PUFA incorporated in phospholipids. No such deficiency or oxidative changes were present in monkeys fed the fish-derived ω -3 PUFA.

At present there are sufficient epidemiological data to indicate that dietary factors play an important part in determining both the symptoms of asthma and bronchial hyperreactivity in adults. There are also *in vitro* data indicating that anti-oxidants and PUFA can influence Th-cell differentiation towards the Th-2 phenotype and thus have the potential to promote the atopic state. We feel that there is enough evidence to justify epidemiological and immunological investigations into the possible role of dietary factors in the aetiology of asthma and its observed increase, and we are currently addressing these issues in a large pregnancy cohort.

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