Role of viral infections in the inception of asthma and allergies during childhood: could they be protective?

In 1983 Gregg[1] reviewed a long list of population surveys from all over the world on the prevalence of asthma and asthma-related syndromes. He observed that at least two patterns emerged from the data: (1) prevalence rates varied widely between populations by factors of up to 10 000; and (2) prevalence rates tended to be higher in populations with better medical care and higher socioeconomic conditions and hygiene standards. He also pointed out that the prevalence of asthma seemed to have increased during the preceding decades in populations living in more developed countries with a "western" lifestyle. In subsequent years the stream of asthma surveys has consistently increased, but the patterns described by Gregg have not changed and, if anything, have become more accentuated. Studies now show that up to one quarter to one third of all young schoolchildren in the UK[2] and Australia[3] have recurrent wheeze, and almost half have at least one positive skin test to aeroallergens.

Two articles in this issue of *Thorax* compare the prevalence of asthma in different population samples. Flynn[4] reports a higher prevalence of frequent wheeze in children of Indian origin from rural Fiji than Melanesian Fijian children living in the same area. Leung and Ho[5] found significantly lower prevalence rates of asthma and allergic sensitisation in Chinese children living in mainland China than in children of similar origin living in westernised Hong Kong, whereas Chinese children living in Malaysia had intermediate prevalence rates. As with many other similar studies, the differences observed in both reports remain largely unexplained.

Asthma and the environment

It is possible that language barriers and cultural variations in understanding illness and interpreting symptoms may partially account for the striking differences in the prevalence of asthma between populations such as those studied by Flynn and by Leung and Ho. There is strong evidence that genetic factors influence the expression of asthma,[6] and differences in the frequency of the genes responsible for asthma between populations may also have a role. In western countries increased knowledge about asthma among both physicians and parents in the last 20 years may have made the label of "asthma" more common, thus apparently increasing its prevalence. However, although all these factors may have an influence, there is strong evidence to support the hypothesis that the increases in the prevalence of asthma in the western world are real, and that environmental factors play a crucial part both in these increases and in the differences in asthma prevalence between populations and ethnic groups.

Particularly revealing in this sense are the studies comparing prevalence of asthma, bronchial hyperresponsiveness, and allergy skin test reactivity between children of the former East and West Germany.[7] These two populations speak the same language and have similar genetic background, but lived in very different social systems for over 40 years until the country was reunified in 1989. Surveys performed shortly thereafter showed that West German children had a higher prevalence of asthma, bronchial hyperresponsiveness, and allergic sensitisation than East German children, while symptoms of respiratory infection were more frequent in East Germany.

These results seem to confirm observations made many years earlier among migrant populations in the UK. In the late 1960s Morrison Smith *et al*[8] reported that the prevalence rates of asthma in Asian and West Indian children who had been born in the UK were very similar to those of English children. However, prevalence rates in immigrant children who had been born in their countries of origin were generally much lower than those of children born in the UK. These data suggested that environmental events occurring very early in life, perhaps shortly after birth, could explain the findings. Other studies of children immigrating to more westernised societies[9,10] confirmed the observation that these children had a much higher prevalence of asthma and allergic conditions than those who remained in their home countries.

Role of outdoor pollution

The environmental factors responsible for these changes have not been elucidated. For the last three or four decades the role of air pollution in the inception of asthma has been a matter of considerable scrutiny. Although there is some evidence to suggest that outdoor air contamination may provoke symptoms in persons who already have asthma,[11] there is no proof that air pollution increases the likelihood of developing asthma in susceptible subjects. If anything, the contrary seems to be true. Prevalence rates of asthma, atopy, and bronchial hyperresponsiveness were significantly *lower* in Leipzig, East Germany, where children were exposed to high levels of sulphur dioxide, than in the much cleaner Munich in West Germany.[7] Similarly, the prevalence of asthma was considerably lower in the heavily polluted Guangzhou area in continental China[12] than in the less contaminated city of Hong Kong.[5] Exposure to vehicle exhaust is more common in western societies, and could induce asthma in subjects who had not had it previously. However, Gregg[1] has convincingly argued that, if this was the explanation, significant differences in the prevalence of asthma between urban and rural communities should be expected, and the paper by Flynn in this issue of *Thorax* clearly shows that this is not the case.

Role of indoor exposure

Exposure to indoor pollutants in western societies has also been incriminated as an inducer of asthma, but again the evidence seems to point precisely in the opposite direction. The use of wood stoves is extremely rare in western societies nowadays, but was very common in the highlands of New Guinea where Anderson first described an exceedingly low (0·007%) prevalence of childhood asthma in the late 1960s.[13] This finding was confirmed 10 years later by Woolcock, albeit with an increase in prevalence to a still very low 0·6%, the discrepancy probably being attributable to the different methodologies used.[14]

Exposure to tobacco smoke in early life has increased steadily in the last decades mainly because more women of childbearing age have taken up smoking. Passive smoking has been associated with an increased risk of developing

asthma in childhood, but these effects require heavy exposure and seem to be less likely among the better educated families in the developed countries[15] where prevalence of asthma has steadily increased. Considerable attention has been paid to exposure to aeroallergens in early life,[16] but no conclusive evidence exists to show that exposure to house dust mites or other indoor allergens has increased in the last 40 years in the western world, or is more prominent than in societies with other lifestyles and lower asthma prevalence rates.

Role of respiratory infections

One of the most consistent (and most overlooked) observations in studies of the prevalence of asthma is the inverse relation between asthma and the incidence of respiratory infections. In his classic studies in New Guinea Anderson observed that respiratory infections were more common among young children in the Highlands, where asthma prevalence was exceedingly low, than in the coastal regions of the country, where asthma occurred more frequently.[17] As stated earlier, more recent studies by von Mutius *et al*[7] suggested that respiratory infections were more common in East Germany than in West Germany, whereas asthma and allergies were more frequent in the western part of the country. The same pattern seems to prevail among the two ethnic groups in Fiji, as previously described by Flynn.[18]

Asthma in Tristan da Cunha and in the Western Carolinas

Perhaps the most interesting observation in this sense is that of the very high prevalence of asthma on the remote island of Tristan da Cunha and in the Western Carolina islands.

Located halfway between Africa and South America in the Atlantic, Tristan da Cunha is inhabited by a stable population of less than 300 persons who, until recently, rarely left the island and who are mostly descendants of 15 original settlers. In the 1940s the prevalence of asthma in the island was estimated at 46%,[19] perhaps the highest described for any population in the world.

For years the prevailing hypothesis was that genetic factors explained this very high prevalence of asthma; the population is highly inbred and it is believed that some of the original settlers had asthma.[19] In 1961, however, a volcanic eruption forced the islanders to evacuate the island and to transfer to the UK. Shortly after the evacuation blood samples were obtained from many islanders and immunoassays revealed a low prevalence of serum antibodies against common viruses.[20] This should have come as no surprise since a medical practitioner stationed in the island up to the time of the eruption had observed a very low frequency of severe respiratory infections, and well defined epidemics of colds were only observed with the arrival of the few ships that visited the island.[21] However, intestinal worm infestation was almost universal. During the two years they lived in the UK the most striking change which occurred in the health of the islanders was the very high incidence of respiratory infections. Children examined during that period were described as healthy but perennially affected by rhinorrhoea and other manifestations of respiratory illness.[22] Several years later, after most had returned to the island, Mantle and Pepys[19] observed that the prevalence of asthma among the Tristanians was still above 20%, and that sensitisation to aeroallergens was very frequent, affecting almost half the population. The evidence thus supported the contention that a population with an extremely high prevalence of asthma and a high prevalence of allergic sensitisation had a very low incidence of respiratory infections while living on their remote island, and became heavily infected after being exposed to respiratory viruses that they had probably rarely encountered before.

The case of the Western Carolina Islands is remarkably similar to that of Tristan da Cunha. These Micronesian islands are located in the Pacific Ocean approximately 1000 miles north of Papua New Guinea. They are remote and isolated, and a high degree of inbreeding is present in their population. In 1964 Brown *et al*[23] studied serum samples obtained from the islanders before and after a severe epidemic of influenza. They found an almost total absence of pre-epidemic antibody to types A and B influenza virus. The authors suggested that the islands were so isolated from the rest of the world that viral infections were probably very uncommon and mainly related to the infrequent visits of ships from the closest islands. Brown and Gajdusek[24] later observed that one third of the population of the islands suffered from asthma, and an extraordinary 75% prevalence of asthmatic symptoms was present in young children. Again, much as in Tristan and in New Guinea, infestation with intestinal parasites was almost universal, and this obscures the meaning of the very high levels of IgE reported by Brown and Gajdusek among Western Carolinian asthmatic subjects.

Inhabitants of Tristan de Cunha and of the Western Carolina Islands were thus immunologically at the Antipodes with respect to those of the Highlands of New Guinea and, for that matter, of most children of the Third World, who are usually heavily burdened with respiratory infections but have a low prevalence of asthma and allergies. Standards of living, parasite infestation, access to medical care, and environmental contamination were all similar to the three locations and therefore could not explain the striking differences in asthma prevalence observed between the remote islanders and their New Guinean counterparts.

Number of siblings and allergies

Two recent studies have provided further support to the hypothesis that viral infections in early life may play a part in the prevention of allergic sensitisation. Strachan[25] observed a striking inverse relation between the prevalence of allergic rhinitis and the number of older siblings in a large population sample from the UK. Interestingly, no association was found between allergic rhinitis and the number of younger siblings in the family. The author suggested that respiratory infections brought about by the presence of older siblings in early life could hamper the development of allergies. Von Mutius *et al*[26] observed that the prevalence of atopy (as assessed by the presence of at least one positive skin test to aeroallergens) was inversely related to the number of siblings in the household among both East and West German children.

These findings, together with the paradigm of higher prevalence of asthma and allergies in populations in which incidence of respiratory infections is low due to their isolation, suggest a possible explanation for the increases in the prevalence of asthma and allergies in the Western countries. These countries are indeed characterised by a sharp decline in family size, by larger and less crowded homes, and by less contact of children with relatives other than their parents and (if any) siblings. Moreover, prevention of infection is tantamount of modern preventive pediatrics, and mothers, when in need of day care, increasingly prefer smaller settings which have been shown to decrease the likelihood of infection.[27] It is thus possible that these radical social changes may have decreased the incidence of respiratory infections in early life among children of western societies, not to the extremes observed in

Tristan da Cunha or the Western Carolinas, but enough to somehow alter the balance between infection and asthma in favour of the latter.

Ontogeny of T cell function

This hypothesis would have remained as nothing more than speculation without a reasonable biological basis that could support it, were it not for the explosive development in recent years of new knowledge about the ontogeny of the immune system in early life. The picture that emerges is far from complete, but it provides new insights into the factors that regulate both the immune response to infection and development of IgE-mediated reactions.[28]

The evidence indicates that two mutually exclusive T helper cell phenotypes develop from a common ancestor cell. Th1 cells produce interferon gamma and interleukin 2 (IL-2) but not IL-4 or IL-5, whereas Th2 cells produce IL-4, IL-5, and IL-10, but not interferon gamma or IL-2. IL-4 is one of the necessary signals that induce B cell clones to switch from IgM-producing to IgE-producing cells. Interferon gamma, on the other hand, is a potent inhibitor of IgE production by B cells, while IL-10 inhibits the development of Th1 cells. Not surprisingly, infants who will develop positive skin test reactivity to allergens later in life have less interferon-producing cells in peripheral blood than those who will not develop allergies (Martinez *et al*, submitted).

Genetic factors influence the relative presence of the components of peripheral blood, with children of atopic parents having less interferon gamma-producing cells than those of non-atopic parents (Martinez *et al*, submitted). Environmental factors may also exert their influence as interferon gamma is produced in high quantities during certain infections.[28] It is thus plausible to surmise that repeated viral infections, particularly during early life, may selectively enhance the development of Th1-type cells, thus inhibiting the proliferation of Th2-like clones and the development of allergic sensitisation. Conversely, in susceptible subjects less exposed to respiratory infections, Th2-like clones would be preferentially activated, with increased production of specific IgE against aeroallergens and increased prevalence of asthmatic symptoms.

Conclusions

There is little doubt that more than one environmental factor will be found to be responsible for the differences in the prevalence of asthma observed between populations, and for the temporal changes in prevalence observed within populations. The hypothesis of a preferential selection of Th1 clones by recurrent early life infections with subsequent inhibition of allergic sensitisation offers a coherent framework in which to insert observations such as those of Flynn and Leung and Ho, but requires further evidence and, even if confirmed, does not entirely solve the puzzle. Flynn, for example, reported similar prevalences of atopy (as assessed by skin tests) among Fijian Indians and Melanesian Fijians, in spite of a higher prevalence of bronchial responsiveness and a higher incidence of severe asthma in the Fijian Indians, and a higher incidence of respiratory infections in the Melanesian Fijians.[18] No information was available, however, on the age at which allergic sensitisation had first occurred. Peat *et al*[29] have shown that only sensitisation occurring in early life is associated with a higher risk of asthmatic symptoms, whereas subjects sensitised in late childhood were no more likely to have asthma than non-atopic children.

It is thus possible that viruses may exert their influence on the determination of T helper phenotypes during the first months after birth when the immune system is immature and thus more amenable to change. Perhaps a better understanding of the ontogeny of the immune system in early life will help us to elucidate the complex interactions between genetic susceptibility and environmental influences which occur at the onset of asthma.

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