

Editorial

‘Grabbing the bull by the horns’ for allergy prevention

As prevalence rates for allergic diseases have risen progressively, initially in the developed but now also the developing world, there has been an exponential increase in publications outlining investigations of the early life origins of allergy and attempting to identify causes for the increased prevalence. Interspersed amongst these studies are a few that have taken the plunge and moved from observational studies to intervention. However, these latter studies have not been without problems and surprises. Indeed, this is the subject of a review in this and the next three issues of the Journal in relation to dietary intervention.

The great difficulty in moving from observations to intervention is that almost inevitably the information from observational studies is incomplete and understanding about basic mechanisms is too simplistic and currently also incomplete. Thus there is always the potential that an intervention will do harm. Indeed, I believe this is the reason why no one has yet ‘grabbed the bull by the horns’ in relation to immunotherapy as a means to reduce allergic disease. There is a clear concern that by reducing Th-2 responses, Th-1 activity will be upregulated thereby leading to an increase in Th-1 associated diseases such as insulin dependent diabetes mellitus. We now begin to understand more about the regulation of both Th-1 and Th-2 activity and have epidemiological evidence that Th-1 and Th-2 diseases co-exist more frequently than by chance. Thus by inducing a more effective regulatory process, it may be possible to reduce risks of both Th-1 and Th-2 associated diseases and perhaps the time has come to begin immunomodulatory intervention studies in early life.

Unfortunately the simplistic approach of introducing allergen avoidance as a strategy to reduce the risk of allergy has yielded very disappointing outcomes. Despite enormous effort, the best that has been achieved has been

a transient reduction in food allergy and atopic dermatitis in infancy where intensive dietary and other environmental measures have been employed. Furthermore, more recent studies have suggested sometimes that very high dose allergen exposure will induce a modified Th-2 response and thereby tolerance. A relatively old study of rye grass immunotherapy continued during pregnancy suggested that this might reduce allergy in offspring and, therefore, it may be more appropriate in an allergen modification strategy to expose the fetus and infant to high doses in some form of immunotherapy type strategy. Furthermore, data now emerging from house mite avoidance studies during pregnancy and early life are suggesting that while there might be a reduction in wheezing in the first year or two, there is a paradoxical effect on allergen sensitisation. Whether this is a consequence of low doses being more likely to sensitise or is because the environment is modified in some other way remains to be established. Clearly by reducing exposure to house mite, it is also likely that exposure to endotoxin and other microbial products in the dust is also reduced. Are we, therefore, removing a modulatory influence?

The hygiene hypothesis has now been around for well over ten years with numerous studies, suggesting that reduced exposure to a range of microbial products is associated with a higher risk of allergy. There are animal and human studies demonstrating that exposure to appropriate microbial factors reduces allergy and sometimes improves disease. There have even been one or two attempts at controlled trials of prevention with probiotics. However, we have yet to see a proper controlled trial of the use of neonatal BCG or other forms of immunisation such as with *mycobacterium vaccae*. How long should we wait before commencing such studies? There are two papers in this Issue on the use of probiotics, one investigating it mechanistically and the other a small controlled trial in allergic

rhinitis. Our interests should now focus on prevention with such strategies.

The relationship between parasite exposure and allergy is complex. Again, renewed interest recently suggests that there is an inverse relationship. Two papers in this Issue elaborate on this. We do need to understand which parasite antigens are orchestrating a protective response. Clearly it is not just a consequence of flooding the system with parasite specific IgE. A component of the immune response to eliminate parasites is Th-1 mediated and clearly there are also effects on regulatory cells. Further investigation is required in this area as well.

It has become clear that dietary influences on allergy do not only relate to allergen exposure but also to fundamental nutrition and how this affects immune responsiveness. One paper in this Issue has investigated dietary essential fatty acid supplementation, admittedly in a murine model. However, there are now trials in progress investigating the use of dietary supplementation as a means of improving nutrition and thereby immune responsiveness in mother, fetus and newborn. The difficulty is in knowing which dietary factors are critical. My own prejudice is that those factors which affect membrane phospholipids will be particularly important in

affecting receptor aggregation in lipid rafts on the cell surface, signal transduction and intracellular events. Should we now commence a series of controlled trials of particular dietary supplements or should we concentrate further on elaborating the mechanisms?

The other ingredient that has not been considered in the overwhelming majority of studies so far published is the influence of genotype in relation to specific environmental experience. It is almost inevitable that the impact of specific interventions will be influenced by genotype. Thus, perhaps we should await clearer elaboration of the functionally relevant genetic polymorphisms which affect susceptibility to allergic sensitisation in relation to specific environmental exposures.

We all work on the Hippocratic principle to first do no harm but I believe the often misplaced anxieties of clinical researchers has sometimes imposed massive delays on proceeding from observation to intervention. Given the enormous health economic burden of allergic disease in our communities, may be we should now be 'grabbing the bull by the horns'.

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