

URBANISATION AND IMMUNOGENETIC PROFILES: THEIR INFLUENCE ON ALLERGIC SENSITISATION AND ON INTERVENTIONAL STRATEGIES FOR ALLERGY PREVENTION

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There are pivotal, Eureka moments in all of our lives. Moments which change the course of our futures and define our legacy. Some are more easily identified than others, but all have that unique capacity to leave a strong footprint on the evolving story of our lives.

Such a moment presented itself to me when I first met Professor Eugene Weinberg. It was 1982 and I was working in the Outpatients Department at the Red Cross War Memorial Children's Hospital in Cape Town, waiting for a Registrar's post in Paediatrics. I had developed an interest in allergic disease while in private general practice in Stellenbosch in the mid 1970's and was one of the first to begin skin testing with the then Bencard range of allergen extracts in my consulting rooms. I had the idea that we should open up an Allergy Service in Outpatients, to ease the load on the very small but unique and renowned Allergy Clinic run at the hospital by Eugene (then still Dr Weinberg!). It would typically take up to two months for our outpatients to get an appointment at the Clinic, whereas we could see allergic children within a few hours in Outpatients, if adequate human resources were allocated to such a service.

Eugene wholeheartedly supported the idea and the Red Cross Outpatient's Allergy Service was created and still continues to render a much valued service today, thirty two years later. More significantly, however, is that it was the beginning of a deeply meaningful friendship and collegial academic relationship between Eugene and I, resulting in 32 years of pivotal academic research, the publication of seminal high impact papers and a doctoral thesis, a contribution to the exponential growth and recognition of allergy as a credible sub-speciality through our mutual roles in the Allergy Society (together with numerous other pioneering colleagues) and the success of many other exciting projects. Today we continue to work together as

co-editors for this journal.

At that time, we had noted that there had been a well-documented increase in all forms of allergic disease during the preceding fifty years. An increase in asthma per se was also observed, reflected not only by an increase in hospital admission rates, but also in asthma mortality and the presence of an unexpectedly high incidence of bronchial hyper-responsiveness in certain population groups, as demonstrated in the clinic and also by Histamine Bronchial Provocation Testing in our field studies.

Of interest in these epidemiological studies was the fact that indigenous populations in developing, emerging countries (the so-called Third World countries) had historically manifested a very low prevalence of asthma and other allergic diseases when compared to Western, developed First World countries. Nevertheless, the exponential increase in allergic diseases seemed to be occurring predominantly in these very same 'emerging' Third World countries, but where the traditional rural and tribal lifestyles of the indigenous populations had been abandoned as a result of rapid urbanisation to the cities, in search of a better life.^{1,2} In these newly established informal settlements surrounding the big cities, similar to the favelas in South America, the newborns of these migrant families had been rapidly exposed to a Western and First World lifestyle switch, overnight as it were, as their mothers and extended families sought employment and scarce financial remuneration in the urban environment. Very quickly, it would seem, their traditional and centuries-old practices in raising their children were abandoned because of new values and the practical implications of their will to carve out a better life for themselves. For instance, in these migratory populations, breastfeeding is typically abandoned while the mothers are away at work, the exposure to industrial pollution is unavoidable, their dietary habits change

immediately, they become urbanised and their virgin exposure to ubiquitous and novel allergens become new realities.^{3,4}

This situation fascinated me in the early 1980's. Eugene Weinberg, the late Prof 'Boet' Heese (Professor and Head of Paediatrics at the time) and I believed that these migrant urbanising populations presented a unique opportunity to assess the immunological, genetic and environmental factors responsible for the observed dramatic increase of allergic disease in these communities. I recognised that these 'urban-naïve', migratory Black neonates and infants, when compared with the more stable and settled Mixed and Caucasian neonates and infants in Cape Town as comparative controls, could show some unique and important differences in both their clinical and their immunological profiles.

Together with our team of researchers at the Red Cross Children's War Memorial Hospital in Cape Town, a line of research was begun to redefine and validate whether the preventative guidelines for allergic disease at that time in the mid 1980's⁵ and the local relevance of alternate potential predictive immunological markers, so eloquently presented by the global pioneers in this field (Professors Kjellman and Bjorksten at Linköping University in Sweden and Professors Jill and John Warner and Stephan Holgate in Southampton), were equally as relevant in our urbanising Black populations. Together with my abovementioned academic mentors and colleagues in Cape Town (also including Professor Paul Potter at the Department of Immunology at the University of Cape Town), these Swedish and English academic giants were unstintingly supportive of our team when we undertook this prolonged work.

The primary purpose of my research theme was four fold:

1. To establish relevant guidelines for the prediction and prevention of allergic disease in infancy for all ethno-genetic groupings in Southern Africa;
2. To identify the role of rapid urbanisation in influencing the epidemiology and expression of allergic disease in previously unaffected populations;
3. To assess various atopic markers at birth to identify the high allergic risk neonate in all ethnic groups;
4. To examine various interventional strategies to abrogate the central stimuli at play in the switch and transition from non-affected infants into affected allergic phenotypes in Southern Africa.

Further studies by our group also showed clearly that the environmental factors at play, before and immediately after birth, were powerful adjuvants which stimulated their already genetically determined, non-specific, high polyclonal IgE levels, causing rapid specific allergic sensitisation in these Black infants. These high-responder IgE genotypes seemed to represent a historical and ontologic phylogenetic and genotypically determined response to the common round worm (*Ascaris lumbricoides*) in their rural environment, but were paradoxically not indicative of an allergic predisposition as seemed to be the case in the Mixed and White control group.⁶ It is in these very same South African Black newborns, once their mothers had translocated to the peri-urban setting, that the rapid escalation of allergic disease was taking place. This strongly suggested that environmental factors, superimposed on the already significantly primed high polyclonal and non-specific IgE load at birth, were the predominant determinants of clinical disease in these urbanising communities. Our studies showed that it rendered the cord blood serum IgE concentrations futile in any predictive sense for future allergic disease in these populations.⁷

These findings began a new wave of interest in re-examining this process of the prediction and prevention of allergic disease at the time. It was also quickly recognised by many scientists around the world that there was a significant cost in the implementation of preventative programmes, amongst these publications being the guidelines published by a World Health Organisation Working Group, of which I was a contributor.⁸ Amongst other findings, it also became clear that ethno-genetic and socio-economic influences were not only influential in terms of cord blood IgE values at birth, but also affected other biochemical molecules such as mineral elements in cord blood, including plasma copper, caeruloplasmin, zinc and selenium.⁹ Normal values consequently needed to be established for a host of other biochemical markers in the different ethnic and socio-economic groups in any particular clinical situation before any meaningful and significant conclusions could be reached regarding their clinical interpretation.

Other prospective surrogate cord blood atopic markers, such as the total unactivated eosinophil counts,¹⁰ circulating platelets¹¹ and anti-bovine cow's milk specific IgG¹² were investigated by our team at birth and throughout infancy, as well as the adjuvant effect of the trivalent DPT (Diphtheria, Pertussis and Tetanus) vaccination in infancy in terms of the subsequent development of specific anti-Bordetella pertussis IgE antibodies and allergic disease.^{13,14} An in-depth

examination of the Th1 lymphocyte derived Interferon Gamma and the Th2 lymphocyte derived Interleukin 4 and 5 cytokine ratios in Black asthmatic and normal children in Cape Town were also studied by our team as part of this work.^{15,16}

The findings of our studies have significantly changed the South African and global thinking regarding the use of cord blood IgE and other potential surrogate allergic markers in terms of their predictive relevance in various mixed populations around the world.¹⁷ Our research conclusions, while not always popular at the time in the Western World, were published over a period of two decades. I clearly remember a World Allergy Congress in Montreaux, Switzerland, in 1988, when most of the audience left the presentation theatre when Eugene and I delivered our talks. Those were the apartheid days, and we were not welcome anywhere at the time!

Nevertheless, our work established important step changes in the field of allergy prediction and prevention,¹⁸ amongst which is the recognition that an allergic family history is still the best predictor of the allergic phenotype.

I was truly blessed to experience those 20 years of wonderful academic collegiality, friendship and science.

A truly Eureka era!

REFERENCES

- 1) Haus M. An epidemiological shift in allergic sensitisation in a South African Black urbanising community. Proc Annual Meeting of the European Academy

- of Allergy and Clinical Immunology. 12-15 September, 1993. Rotterdam, Holland.
- 2) Haus M. Allergic sensitisation and urbanisation. Issues in Medicine. S Afr Med J 1993;83:238-241.
- 3) Haus M. Urgent dietary intervention required in urbanising communities to prevent allergy epidemic. S Afr Med J 1992;81:117.
- 4) Haus M. Allergy in South Africa. S Afr Med J 1994;84:466-468.
- 5) Haus M. Prevention of allergic disease. S Afr J Cont Med Ed 1987;5:37-47.
- 6) Haus M, Heese HdeV, Weinberg EG, Potter PC, Hall JM, Malherbe D. The influence of ethnicity, an atopic family history and maternal ascariasis on cord blood serum IgE concentrations. J Allergy Clin Immunol 1988;82:179-189.
- 7) Haus M, Heese HdeV, Weinberg EG, Potter PC, Hall JM, Malherbe D. Genetic and environmental influences on cord blood IgE and on atopic sensitisation in infancy. S Afr Med J 1990;77:7-13.
- 8) Weiss K, Haus M, Iikura Y. The costs of allergy and asthma and the possible benefit of prevention strategies. In: World health Organisation (WHO) Project Report and Guidelines. 2003. Ch.5:184-192.
- 9) Heese HdeV, Haus M, Dempster WS. The influence of ethnicity on plasma copper, caeruloplasmin, zinc and selenium concentrations of Cape Town mothers in term and their infants. Paediatric Nutrition. ISPEN 1999;1:25-36.
- 10) Haus M, Hall JM, Heese HdeV, Weinberg EG, Berman D. Cord Blood and maternal total eosinophil counts in relation to infant allergy. Paediatr Allergy Immunol 1992;3:23-27.
- 11) Haus M, Heese HdeV, Weinberg EG, Hall JM. Cord blood eosinophils and platelets as predictive atopic markers. Clin Exp Allergy 1990;20:10.
- 12) Haus M, Weinberg EG, Heese HdeV, Hall JM, Potter PC, Scott RAD. Cord blood anti cow's milk IgG and IgE as atopic markers in Third World Black and White newborns. S Afr J Science 1989;85:409.
- 13) Haus M, Weinberg EG, Malherbe D. Specific IgE antibodies to Bordetella pertussis after immunisation in infancy. Lancet 1988;1:711.
- 14) Haus M, Weinberg EG. Specific IgE antibodies to Bordetella pertussis after immunisation in infancy. Lancet 1988;1:1393.
- 15) Nurse B, Haus M, Puterman AS, Weinberg EG, Potter PC. Reduced interferon-gamma but normal IL-4 and IL-5 release by peripheral blood mononuclear cells from Xhosa children with atopic asthma. J Allergy Clin Immunol 1997;100: 662-668.
- 16) Nurse B, Puterman AS, Haus M, Berman D, Weinberg EG, Potter PC. PBMC's from both atopic asthmatic and non-atopic children show a Th2 cytokine response to house dust mite allergen. J Allergy Clin Immunol 2000;106:84-91.
- 17) Haus M. The current status of allergy prediction and prevention in infancy using in vitro assays. In: In-Vitro Testing. Thieme Medical Publishers, Inc.1994. Ed. Ivor A Emanuel. The American Academy of Otolaryngic Allergy. AAAO Monograph Series. San Francisco. 84-96.
- 18) Potter PC, Green RJ, Haus M. Prevention of Allergic Disease. In: ALLSA Handbook of Practical Allergy. Third Edition. The Allergy Society of South Africa 2010; 212-217.