Further consideration of the study ‘Bronchial hyper-responsiveness and atopy in urban, peri-urban and rural South African children’

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ABSTRACT

Over two decades ago, the prevalence of sensitisation to allergens and asthma in rural Xhosa children was very low, as documented in the seminal studies of Profs Van Niekerk and Weinberg et al. This article reviews a recent study published in Pediatric Allergy and Immunology, which examined the bronchial hyper-responsiveness and atopy in urban, peri-urban and rural South African children, the last group from an area in the rural Transkei where the original study of Van Niekerk et al. was conducted 20 years ago.

Bronchial challenge with histamine demonstrated that 17% of rural and 34.4% of recently urbanised Xhosa children had increased BHR, a marked increase from the 0.03% and 3.17% prevalence of increased BHR previously reported by a study using exercise challenge. The prevalence of increased BHR in white urban children from the ‘pollution-free’ area was 33%, and from the ‘high-pollution’ area 56.6%.

Sensitisation to one or more aero-allergens, as indicated by CAP RAST tests, was present in 36.6% of the rural Xhosa children with normal BHR and in 62.5% of those with increased BHR. Atopic sensitisation to one or more aero-allergens, as indicated by skin-prick test, was found in 42.3% of the recently urbanised Xhosa children and 45% of the urbanised white children. This study also recorded, for the first time, sensitisation to house dust mites (HDM) in rural Xhosa children.

The study found that increases in BHR in the rural and recently urbanised Xhosa children develop independently of increases in atopy. These results are compared to a very high prevalence of BHR in urban white children from the ‘high-pollution’ group, which is reported in this review. The findings of the questionnaire will not be reviewed in this article.

INTRODUCTION

The following is a summary with additional commentary of an article that appeared in Pediatric Allergy and Immunology (PAI) in October 2003.1

Over two decades ago, the prevalence of sensitisation to allergens and asthma in rural Xhosa children was almost unheard of, as documented in the seminal studies of Van Niekerk et al.2 Recently, PAI published our findings examining the bronchial hyper-responsiveness (BHR) and atopy in urban, peri-urban and rural South African children, documenting the rising prevalence of these conditions in various groups and reporting a dramatic increase of atopy in rural Xhosa children.3 The findings of this paper are reviewed here and contrasted with a fourth publication of the study, not published before, which examined BHR in a group of children living in an area in close proximity to a petrol refinery, which documented a disproportionately high prevalence of BHR.

One thousand four hundred and fifty-seven school children aged 10-14 years, from the rural Transkei, from a recently urbanised peri-urban area, and from urban Cape Town areas, were studied using a questionnaire. Seven hundred and forty children had histamine challenges, and 573 tests for atopy were also conducted.

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Sensitisation to one or more aero-allergens, as indicated by CAP RAST tests, was present in 36.6% of the rural Xhosa children with normal BHR and in 62.5% of those with increased BHR. Atopic sensitisation to one or more aero-allergens, as indicated by skin-prick test (SPT), was found in 42.3% of the recently urbanised Xhosa children and 45% of the urbanised white children. This study also recorded, for the first time, sensitisation to house dust mites (HDM) in rural Xhosa children. Passive cigarette smoking was not identified as a risk factor for increased BHR or atopy. Wood smoke in the indoor environment did not play a role for the rural Xhosa children. Ascaris infection did not play any modifying role in the development of increased BHR in the rural or urban children.

The study found that increases in BHR in the rural and recently urbanised Xhosa children develop independently of increases in atopy. These results are compared with a very high prevalence of BHR in urban white children from the ‘high-pollution’ group, which is reported in this review. The findings of the questionnaire will not be reviewed in this article.

The PAI article needs to be viewed in context. Asthma is the commonest chronic childhood illness in developed communities. Its prevalence has markedly increased during the past two decades. The prevalence of asthma has been reported to be far lower in developing countries.1 Earlier studies of South African black children reported that asthma was a rare condition. The admission rate for black children with asthma to a then black hospital (King Edward, Durban) was 0.002%, compared with 0.79% for white children admitted to a then white hospital (Addington, Durban).2

In 1979 Van Niekerk et al.3 using exercise challenge tests, found the prevalence of asthma in Xhosa children in a rural village in the Transkei to be 0.14%, compared with 3.1% in peri-urban Xhosa children near Cape Town. HDM sensitivity was not found in the rural asthmatics, but a 65% prevalence was reported for the city asthmatics. Since the children were from the same tribe, researchers attributed the difference to environmental rather than genetic differences, and specifically to urbanisation. As recently as 7 years ago, Potter et al.4

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found no specific IgE to HDM in a study of Transkei rural Xhosa children. Although longitudinal studies have shown striking increases in asthma in certain populations, cross-sectional studies also show striking differences in ethnically identical populations. To explain differences in the prevalence of asthma between ethnically identical societies in the previous East and West Germany, a ‘hygiene hypothesis’ has been advanced by Von Mutius et al.¹ This article reviews our findings ¹ which were obtained by travelling to the same rural Transkei area 20 years after the original studies of Van Niekerk et al.²

**METHOD**

**Selection of children**

Children aged 10-14 years living in four types of environment were compared: traditional rural Xhosa, more affluent rural Xhosa, recently urbanised Xhosa, and fully urbanised white children.

Five different areas were compared. Children were recruited from geographically and environmentally distinct localities for the histamine challenges: two areas in the Libode district of the Transkei, and Marconi Beam, Kirstenhof and Table View in the Cape Town area.

The rural Xhosa-speaking children were from an area of Transkei within 60 km of the area previously studied by Van Niekerk et al. (where a low prevalence of asthma was found). Xhosa children studied there were living either in a very poor rural environment – essentially unchanged from 20 years ago (the area around Ntlaza School) – or in a more affluent rural environment (the one served by Mt. Nicholas Catholic School). The urban group of Xhosa children had recently (within the past 14 years) migrated to a Cape Town peri-urban squatter area (Marconi Beam). The white (Caucasian) children were from two city suburbs: one near a petrol refinery (Table View), and one in a pollen-rich area (Kirstenhof).

**Assessment of the children**

The histamine bronchoprovocation test was used to assess BHR. Children were challenged with histamine according to the modified protocol as described by Yan et al.³ IgE responsiveness in children in the Transkei was determined by measurement of specific IgE by CAP RAST (Pharmacia, Uppsala, Sweden) to HDM, grass mix, cat, dog, and Ascaris. For children residing in the Cape Town areas of Marconi Beam, Kirstenhof, and Table View, IgE responsiveness was determined by SPT for nine common aero-allergens: maize pollen, Bermuda grass, grass mix, tree mix, house dust mite mix, mould, feather, cat, and dog. All extracts, bar one, were manufactured by Miles Inc (Eikhart, Indiana, USA).

**RESULTS**

**Histamine challenge results**

The results of the histamine challenges are summarised in Figure 1. There were no significant gender differences in any of the schools.

**Rural schools – Transkei**

Two hundred and twelve children (121 females and 91 males) were challenged. Seventeen per cent (36/212) had a fall in forced expiratory volume in one second (FEV₁) during bronchial challenge of 20% or greater and were categorised as having BHR (PD₂₀FEV₁ of less than 8 µmols). There was no difference in the prevalence of BHR in the two Transkei schools.

**Recently urbanised school – Marconi Beam**

Ninety-six children (58 females and 38 males) were challenged. A decrease in FEV₁ of 20% or greater during the bronchial challenge was documented in 34.4% (33/96) of this study group, and these subjects were categorised as having BHR (PD₂₀FEV₁ of less than 8 µmols).

**Urban school – Kirstenhof**

Ninety-nine children were histamine challenged (48 females and 51 males). Two girls developed upper airway obstruction with the last dose of histamine and were excluded from further analysis. Thirty-three percent (32/97) had a fall in FEV₁ during bronchial challenge of 20% or greater and were categorised as having BHR (PD₂₀FEV₁ of less than 8 µmols).

**Urban school – Table View**

Two hundred and thirty-nine children (62.6% females and 37.4% males) were histamine challenged. More than 54% of children (139/239) had a fall in FEV₁ during bronchial challenge of 20% or greater and were categorised as having BHR (PD₂₀FEV₁ of less than 8 µmols).

**Atopic investigation results**

The results of the atopic investigations are summarised in Figures 2 to 5.

**Rural schools – Transkei**

Specific IgE greater than 0.3 kU/L to one or more allergens was demonstrated in 62.5% (20/32) of children with positive BHR, and 36.6% (30/82) of those with negative BHR (p=0.022 Yates corrected) (Figs 2 and 3). There was a significant correlation between children with specific IgE greater than 0.3 kU/L to one or more of the aero-allergens and those with specific IgE to Ascaris greater than 0.3 kU/L (p<0.0001). Specific IgE >0.3 kU/L to HDM was found in 37.5% of children with positive BHR and 13.4% with negative BHR (p=0.009). There was no significant gender difference.
There was a significant correlation between a specific IgE greater than 0.35 kU/l to HDM and positive BHR (p=0.009). There was no difference in the prevalence of specific IgE to HDM in the two schools (p=0.69). However, high levels of specific IgE (>17.5 kU/l) to HDM were more common in children attending Mt Nicholas (7/71), compared with those attending Ntlaza School (0/48) (p=0.041). This was not true for grass-, cat- or dog-specific IgE.

A significant difference between the two schools was that children from the Mt Nicholas school had pillows and/or carpets in their bedrooms (p>0.0001). Children who possessed a carpet were significantly more likely to have increased BHR when compared with those who did not (p=0.025 Yates corrected).

Recently urbanised school – Marconi Beam

Twenty-two children (21.2%, 22/104) had wheal formation ≥7 mm² in area to at least one allergen tested for, and 42.3% (44/104) had wheal area size of 5 mm². We have previously observed that in black African children an SPT wheal with an area of 5 mm² or greater than the negative control and accompanied by a flare should be regarded as significant. Figures 4 and 5 demonstrate results of these tests.

Urban school – Kirstenhof

Thirty-six children (45.0%) had wheal formation (7 mm in diameter to at least one allergen tested for, and 47.5% had wheal formation of 3 mm in diameter. There was a significant correlation between BHR and a positive SPT to HDM (p=0.015).

Urban school – Table View

Ninety-three children (50.8%, 93/183) had wheal formation ≥7 mm in diameter to at least one allergen tested for, and 55.2% had wheal formation of 3 mm in diameter. There was a significant correlation between BHR and a positive SPT to one or more allergens tested for (p>0.0001).

DISCUSSION

The PAI study follows that of Van Niekerk et al by almost two decades. The PAI study contrasts a BHR in 17% of rural Xhosa children and in 34.4% of urbanised Xhosa children with that of the Van Niekerk et al study from 20 years ago which found a 0.14% prevalence of increased BHR in rural Xhosa children in a similar region of the Transkei as this study, and a 3.17% prevalence in urban Xhosa children.

In the urbanised white children, the PAI study found the prevalence of increased BHR to be 33.0% in the Kirstenhof children, a relatively low-pollution area of Cape Town. Nagel7 utilised an exercise challenge in a similar group of white children 6 years prior to this study and found the prevalence of BHR to be 5%. Ehrlich et al8 documented that self-reported asthma in a similar group of children in a similar Cape Town community was 10.8% and that the prevalence of wheezing during the prior 12 months was 26.8%. In contrast to the PAI study, Van Niekerk et al2 and Nagel7 measured BHR through a free-run exercise challenge and equated a positive exercise challenge with a diagnosis of asthma.

Results of the BHR of the Kirstenhof group of children (33.0%) are contrasted with the previously unreported BHR of a group residing in a relatively high-pollution area of Table View (54.6%). These results were confirmed by repeating histamine challenges (with histamine from the same batch) on a randomly selected group of children from each school. Mould and pollen counts in both areas were similar, except for a marginally higher prevalence of grass pollen in the Kirstenhof area.

Although exercise challenge has proved to be a useful epidemiological tool for objective measurements of BHR in children, histamine challenges are believed to be more sensitive.9 Exercise challenge and histamine challenges identify different pathways in the airways and other conditions besides asthma may result in an
increased BHR. Therefore although increased BHR cannot be equated with asthma, it does indicate a ‘bronchial hyper-responsiveness’ which may be as a result of other factors, e.g. viral infections. A follow-up questionnaire assessing recent viral infections showed no significant differences between the Kirstenhof and Table View study groups. The increased BHR documented in Table View may be the result of other environmental factors such as pollution. Sulphur dioxide emissions in the area were monitored at the time of the study, and although the mean level of these emissions appears to be within international limits, peaks were recorded that were above these limits. One may postulate that intermittent high sulphur dioxide levels are responsible for ‘chronic’ BHR or that international levels may be outdated and set too high.

A dramatic increase in atopic sensitisation in rural children was reported. Specific IgE greater than 0.3 kU/l to one or more allergens was demonstrated in 62.5% of children with positive BHR, and in 36.6% of children with negative BHR (p=0.02). The PAI study contrasts sharply with a previous study from the same Transkei region in 1990, where no specific IgE to HDM could be detected. The recent acquisition of HDM sensitivity is particularly interesting. The study reported that 7/123 (5.7%) of the subjects had specific IgE to HDM greater than 7.9 kU/l, and that these higher levels occurred in children of a higher socio-economic group. Among the recently urbanised Xhosa children, 21.7% had positive SPTs to one or more of the 9 allergens tested, compared with 47.5% of the urban white children. However, the prevalence of BHR was about the same in these two groups.

In addition to the increases found in the rural Xhosa children, there was an even greater prevalence of atopy and BHR in the urban children. Our study revealed that 29.8% of the recently urbanised black children manifest atopic sensitisation to HDM. Moreover, 37.9% of recently urbanised black children with BHR were SPT-positive to HDM.

Sixty-four per cent of white school children with positive BHR, and 42.5% of all white school children tested, demonstrated sensitisation to HDM. Although in the study groups from the rural Transkei and urban Kirstenhof, a significant relationship was found between BHR and sensitisation to one or more allergens as measured by CAP RAST, as well as between BHR and sensitisation to HDM, we did not observe these same phenomena in Marconi Beam, the location of the recently urbanised study group. Of note was that atopy was determined by SPT in the Marconi children and by CAP RAST in the rural Transkei children. Results from skin tests may not be comparable with results from specific IgE determinations, particularly in the rural populations.

The high prevalence of increased BHR that occurred independently of the presence of atopy in the recently urbanised (peri-urban) group makes it likely that the factors influencing the development of those two parameters are not the same.

Of all households studied, both urban and rural, more than half had at least one member who smoked. We found a significant association between smoking fathers and BHR in the rural study group only. The PAI article argues that both international and local studies have shown that passive smoke exposure from fires for cooking and heating influences the prevalence of lower respiratory tract disease. Children attending Mt Nicholas School were less exposed to smoke from open wood fires, and yet demonstrated the same prevalence of BHR and atopic sensitisation as that found in children attending Ntlaza School. This suggests that other as yet unidentified environmental fac-
tors must be of importance in the development of both atopic sensitisation and BHR.

Concerning the environmental factors that could have contributed to the increase in both BHR and atopic sensitisation in rural black children, it is our opinion that the most significant change to have occurred in the relevant geographical areas is that many homes are now constructed with modern building materials, creating a more closed indoor environment. Although we have not studied this in detail in our questionnaires, it is apparent that the diet of the rural children is different to the typical diet of 20 years ago; there is increased exposure to processed and packaged foods and drinks.

During the past two decades, poor hygienic factors have not shielded rural Xhosa children from a dramatic increase in the prevalence of asthma and atopy. Our study suggests the necessity of considering other recent factors that accompany ‘Westernisation’ – and some of these factors may not yet have been examined in any detail. There are evidently causalities beyond ‘hygiene’ factors to explain the high prevalence in BHR, asthma and atopy in South African children.

Our research also shows that in rural and recently urbanised children, the associations between BHR, atopy and asthma are much weaker than those found in city children. This suggests that different environmental factors influence the development of BHR than those that promote the development of specific allergen responsiveness.

The findings of this study present interesting possibilities for critique of two major hypotheses in allergy: the hygiene hypothesis, and the reliance on the great importance of genetics. As for the former theory, the South African ethnographic and socio-economic environments are well suited for a test. Typically, overall hygiene improves in a culture along with the acquisition of home furnishings conducive to HDM, and this circumstance may confound attempts to distinguish causes. As the survey of rural black Transkei households found, specific, isolated modernisations such as the use of foam pillows and carpets commonly took place with no accompanying striking improvement in household hygiene. (The households were still relatively poor and crowded relative to urban white households, and farm animals were still present.) Therefore, causes other than compromise of the immune system from a more hygienic environment must be sought for increased prevalence of sensitisation. This is supported by the much lower levels of sensitisation in the less affluent Xhosa group studied, who did not have homes likely to foster HDM.

The epidemiological and clinical data on these South African Xhosa children are supported by recent studies of asthmatic Xhosa children by Nurse et al., showing HDM-stimulated T-cell cultures with strong proliferative responses to HDM, and the release of both TH1 (gamma interferon) and TH2-type cytokines, in contrast to the depressed TH1 response observed when the T-cells from the Xhosa asthmatic children are stimulated by mitogen (e.g. phytohaemagglutinin (PHA)) alone. This in vitro research as well as that of others also indicates that the development of specific allergy is not associated with a depressed TH1 response to a given allergen and that TH1 responses may not be protective against the development of clinical allergic responses. If children across the spectrum of allergic disease are developing specific IgE responsiveness and BHR whether they are living in a traditional or modern environment, the role of other changing factors such as diet, social contacts, exercise, immunisation, electrification and medication may be more important and should now be studied in more detail.

The role played by genetics in allergy likewise appears
to be more open to de-emphasis than it has been previously, as a result of the study’s findings. A strong genetic influence on sensitisation has been widely observed to (and, to the extent that it is standard clinical practice, actually does) give warnings for allergen avoidance during pregnancy and early childhood on the basis of one or both parents having allergies. Without throwing genetic factors completely into doubt, new considerations arise from the appearance of evidence of significant increases in atopy in a population whose genetic basis factors appear to remain constant. It should be borne in mind, especially in the light of new findings, that parents and children not only share genes but also tend to share an environment. The special situation in rural South Africa allows a degree of separation of the environmental variant because of the distinctly different environment of the children as opposed to the childhood environment of their parents. This may create clarification of confusing factors when white suburban families are studied, because of the relative stability of Western white material culture over several generations.

However, though a general shift in ideas of allergy causality may be warranted, it is at this point not possible to isolate and definitively test environmental variables. In the circumstances, we are persuaded that HDM sensitisation is important, but the role of diet, for example, cannot be excluded. A recent short communication proposes that aflatoxins contribute to sensitisation and that aflatoxin exposure is particularly high in the developing world. This is of course an extremely interesting hypothesis to us as we examine the increase in allergy in South Africa. Obviously, further study is required.

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REFERENCES