INAUGURAL LECTURE
ALLERGY IN SOUTHERN AFRICA

Paul C Potter, *MD, FCP(SA), DCH(SA), BSc Hons (Immunol), FACAAI, FAAAAI*

Allergy Diagnostic & Clinical Research Unit, University of Cape Town Lung Institute, Observatory, Cape Town, South Africa

Synopsis of Inaugural Lecture following appointment as Full Professor of Allergology at the University of Cape Town

INTRODUCTION

The African continent looks like a huge question mark on the global map. It hides many secrets, raises many questions and provides many answers.

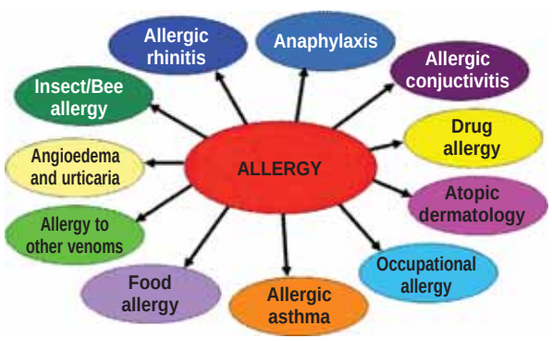
The Egyptian Sun God Ra was considered to be the discoverer of Medicine. The first remedies for asthma are described in the Ebers Papyrus, written about 1550BC and discovered in Thebes in 1862 in a mummy, written in hieratic script. One remedy was a mixture of the dung of the ibis-bird, sweet beer and oil, mixed, boiled and strained, and taken daily for 4 days.

Southern Africa is known to be a region affected by poverty and malnutrition and plagued by AIDS and tuberculosis. These diseases are the major focus in health budgets and research in the region, and rightly so.

ALLERGIES

Numerically speaking, allergies are far more prevalent than TB or AIDS, affecting 25-30% of the population and result in significant morbidity, employment absenteeism, loss of quality of life and in some instances, fatal outcomes. Allergies pose a huge cost to the health sector, affecting all ages, from the poorest to the richest across the geographical spectrum of our region.

THE SPECTRUM OF ALLERGIC DISEASES



Allergy includes underlying major diseases such as asthma and rhinitis and is the direct cause of adverse reactions to drugs, atopic dermatitis, occupational diseases, adverse reactions to foods, hypersensitivity reactions of the skin, angio-oedema and urticaria, insect and bee venom hypersensitivity, conjunctivitis and a number of diseases of eosinophils and mast cells.

Correspondence: Prof PC Potter, e-mail: Paul.Potter@uct.ac.za

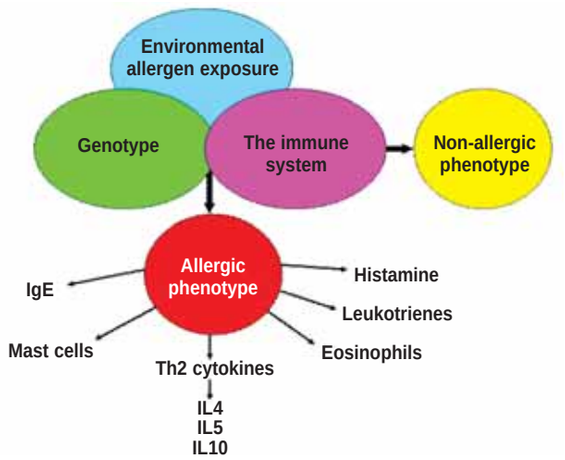
ALLERGIC DISEASE: A TWO-STAGE PROCESS

1. Induction phase

Immune memory following allergic sensitisation, regulated by Th1 and Th2 cytokines and T regulatory networks

2. Effector phase

Expression of disease in the target organ in individuals with variable TH2 directed inflammation



CULTURAL AND ETHNIC DIVERSITY

Southern Africa spans the complete spectrum of human existence, being home to the Khoisan tribes of Namibia and Botswana, numerous African tribes, Caucasians, Indians and immigrants from all over the world.

Superimposed on the vast ethnic genetic and cultural diversity of its peoples is a wide variety of **climatic** conditions (or biomes), a rich diversity of flora and fauna and the rapid migration and urbanisation of its peoples. It is against the backdrop of this change from the old to the new lifestyle that we have observed a dramatic increase in the prevalence of allergens in the region.

Southern Africa may therefore be one of the most interesting parts of the world to study the factors which have contributed to the increased expression of the allergic phenotype worldwide.

It is a notable fact that rural Africans who live in the grasslands or deserts of Southern Africa in traditional accommodation with traditional dietary practices rarely if ever suffer from allergic disease. Asthma for example is so rare among certain peoples of Southern Africa that until recently there was no term to describe the condition in the local idiom, e.g. Xhosa and other indigenous African languages.

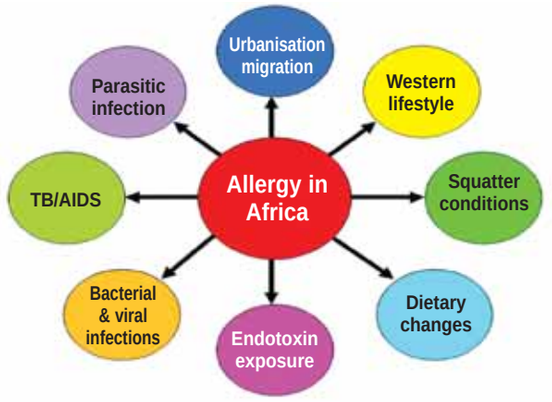
Diseases such as eczema, food allergy and allergic rhinitis are still rare in rural Africans. They were not even mentioned in a health survey of the Bushmen in the Kalahari published in *The Lancet* in 1989 by O'Keefe & Lavender.

A traditional clay, cow dung and thatched African hut, surrounded by grass pollens, wood smoke, chickens, goats, fungal spores and cow allergens would theoretically seem to be the ideal environment for the devel-

opment of inhalant and food allergens. This however is not the case.

Furthermore, parasite infestation (e.g. schistomiasis and *Ascaris* roundworm infestation) which stimulates IgE production (the major antibody-mediating allergy) is also very common in the region, but parasite-infested individuals have been shown (in studies by Von Biggelaar in Gabon) to be protected not from the specific IgE responses to environmental allergens, but from the expression of the allergic disease phenotype.

FACTORS INFLUENCING EXPRESSION OF ALLERGY IN AFRICA



POSTULATED IMMUNOLOGICAL MODIFIERS OF EXPRESSION OF ATOPIC DISEASES

- Early exposure to lipopolysaccharide/endotoxin induces Th1 responses
- Parasites induce IL-10 production via Th2 cells
- Heavy allergen exposure induces tolerance (especially oral route)
- Wood smoke, pollutants may protect
- Exposure to minute doses of allergen in a 'clean' environment tend to 'sensitise'

WHAT DO PUBLISHED STUDIES FROM AFRICA TEACH US ABOUT THE FOLLOWING INFLUENCES ON THE EXPRESSION OF ASTHMA?

1. Hygiene
2. Parasitic infestation
3. Bacterial or viral infection (TB, measles)
4. Urbanisation and migration
5. Diet and body mass index
6. Affluence and Westernisation

EARLY AFRICAN ASTHMA STUDIES (1969-1991)

			Asthma Admission Rate
1969	Wesley *et al.*	Durban Zulu children Caucasian children	0.02% 0.79%

			Asthma Prevalence
1976	Carswell *et al.*	Tanzania Rural children	3.3%
1975	Godfrey *et al.*	Gambia Rural children	3.3%
1979	Van Niekerk *et al.*	South Africa Rural Xhosa *Urban rural gradient*	0.1% 3.1%
1991	Keeley *et al.*	Zimbabwe Rural children Urban children *No differences between black and white*	0.1% 3.2%

CAPE TOWN 2002 (White *et al. Environmental Health* 2009)

Professor Neil White

Recent studies of asthma using a video questionnaire (ISAAC) published in *The Lancet* in 2006 show a prevalence of current asthma symptoms of 20.3% in 13-14 year olds in South Africa. A study by Neil White and colleagues in 2002 found that 23.7% of 3 162 12-year-old children reported ever having had asthma and 64.6% reported hay fever.

Study design

- 3 162 12-year-old children
- ISAAC Questionnaire (video)

Results

- 23.7% reported ever asthma
- 64.6% reported ever hay fever

Conclusion

- Multivariate analysis of symptom-associated factors was positive for:
  - Male gender
  - Family member with asthma
  - Adult smoker in the home
  - Petrochemical emission dose (SO_2)

DECLINE IN TOTAL SERUM/IGE AFTER TREATMENT FOR TUBERCULOSIS[1]

In a study of the interaction between the expression of allergy, tuberculosis and parasite infestation in the Ravensmead area of the Peninsula, published in *The Lancet* in 1999, Adams, Beyers and colleagues reported that the prevalence of parasite infestation, by promoting TH2 protective immunity rather than TH1, may increase susceptibility to tuberculosis, rather than allergy demonstrating a significant decline in IgE values in adolescents treated for tuberculosis.

Study design

- 33 adolescents with TB
- 37 controls
- IgE, Mantoux tests, parasite IgE and SPTs
- Before and after TB treatment

Results

- Significant decline in mean IgE from 457 kU/l to 175 kU/l ($p<0.0001$) which correlated strongly with IgE on presentation ($p = 0.001$)

Conclusion

- Presence of parasite infestation may increase susceptibility to tuberculosis rather than allergy

THE ASSOCIATION OF PROLONGED BREAST-FEEDING AND ALLERGIC DISEASE IN POOR URBAN CHILDREN[2]

Dr Charlie Obihara

A recent study by Obihara and colleagues of a larger sample of 861 children on the possible protective effects of prolonged breast-feeding to prevent allergy

found that allergic disease phenotypes were significantly reduced in those children breastfed for more than 6 months only when there was no maternal history of allergic disease.

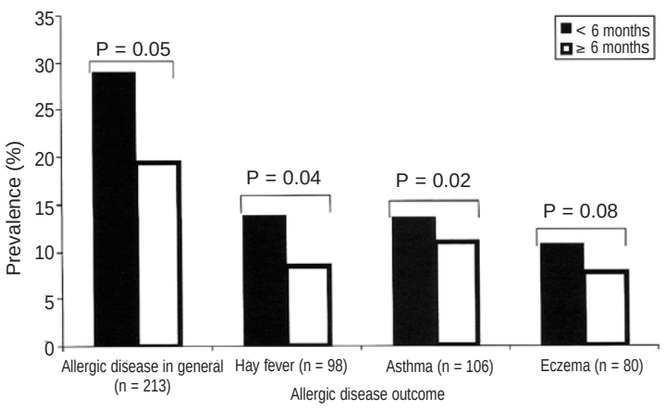
Study design

– 861 children (6-14 years)
– 15% sample of household addresses
– Questionnaire cross-sectional survey ISAAC (Phase 1)

Factors studied

– Breastfeeding duration
– Maternal smoking
– Sibling number
– Maternal education
– Household income
– Infections
– Visits to doctor
– Tuberculin sensitivity

PREVALENCE OF ALLERGIC DISEASE PHENOTYPES IN CHILDREN WITH SHORT (<6 MONTHS) AND PROLONGED (≥6 MONTHS) BREASTFEEDING DURATION



CONCLUSIONS

- Prolonged breastfeeding protects African children whose mothers do not have allergic disease.
- Family history of allergy overrides the protective effects.

ANTHROPOMETRIC MEASUREMENTS, ASTHMA AND ATOPY (2002-2003) (Calvert & Burney, Kings College, London)

Study sample

– 773 Xhosa children with exercise-induced bronchospasm (EIB) (South Africa)
– Case control study

Measurements

– Specific IgE (5 common inhalants)
– Skin-prick tests (11 aeroallergens)
– Body mass index (measured as a standard deviation score (BMISDS)

Results

– Increasing BMISDS associated with an increased risk of EIB after controlling for atopy and income (odds ratio (OR)= 1.74)
– Increasing BMISDS was also associated with increasing IgE and corresponding positive skin tests (p=0.0001; OR=37.9)

• Conclusion

– **FATNESS** increases the risk of EIB

OTHER FACTORS SHOWN TO BE ASSOCIATED WITH INCREASED ALLERGY

1. Increasing wealth
2. Increasing education of the head of the home
3. Combinations of environmental and social variables

XHOSAS IN DIFFERENT ENVIRONMENTS[3]

Bronchial hyperresponsiveness and atopy in Xhosa and white children cross a gradient of environments from rural to urban.

A classic study reported in *Paediatric Allergy and Clinical Immunology* in 2003, conducted by Dr Harris Steinman, examined the influence on geographical location and migration on the expression of allergy and also bronchial hyperresponsiveness, a marker for asthma.

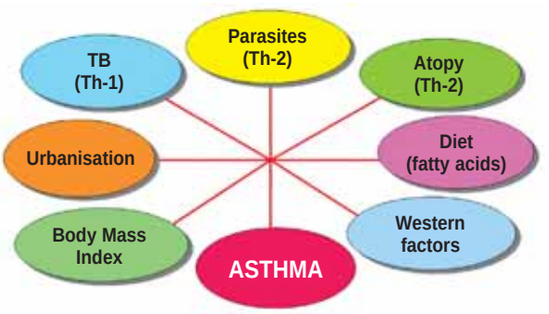
Study groups

– 1 457 children aged 10-14 years
– 2 rural Xhosa environments in Libode area (Transkei)
• *Ntlaza*: traditional rural (huts)
• Mt Nicholas: more affluent rural Xhosa (brick homes)
– Recently urbanised Xhosas in squatter settlements of Marconi Beam, Cape Town (within 4 years)
– Urban white children, one group living near a petrol refinery

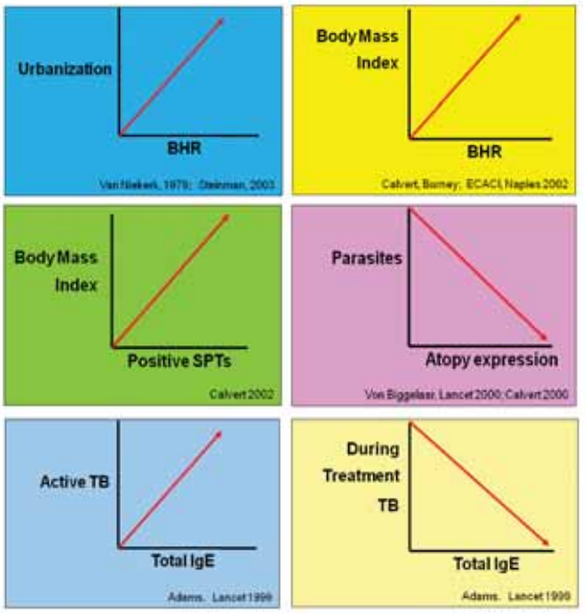
Results

The results of this study showed a gradient between the rural and urban Xhosas, but an increase in bronchial hyperreactivity and specific IgE responsiveness when rural children adopted a more Western life style, which was similar to the prevalence found in children who were born in a Cape Town suburb (Kirstenhof).

LINKS TO ALLERGIES AND ASTHMA: THE AFRICAN EXPERIENCE



THE RELATIONSHIPS OF THESE LINKS AND ASSOCIATES ARE ILLUSTRATED IN THE FOLLOWING GRAPHS:



DISCOVERY OF THE ALLERGENS OF SOUTHERN AFRICA

As early as 1950 Ordman identified a group of asthma sufferers in South Africa who had perennial symptoms at the coast, whose condition was always better inland. He also observed that seasonal allergic rhinitis affected the more affluent South Africans living in the grassland biomes of Southern Africa (e.g. current Gauteng and Tswane).

These original observations laid the foundations for the critical studies by Dutch scientists, Voorhorst and Spieksma in 1964 who confirmed that the house-dust mite *Dermatophygoides pteronyssinus* was the 'factor' causing asthma.

Studies by Gloria Davis (Johannesburg), Ahmed Manjra (Durban) and Farouk Jooma (Cape Town) confirmed high levels of house-dust mites in coastal and inland cities of South Africa, which peaked in late spring in the Cape Town region.

Mrs Dilys Berman & Prof Paul Potter.

The history of kikuyu grass allergy in South Africa goes back 80 years where a single female rhizome was introduced as a pasture grass, originally considered to be non-allergenic. The success of this grass suitable for schools, parks and gardens led to the introduction of male specimens which produced the pollen and hence the allergies. Our local studies have found that while 80% of grass sufferers react to Bermuda and rye some 43% are also sensitised to kikuyu.

Although pollen allergy is predominantly caused by pooideae (rye grass family), Ann Orren and co- workers characterised the *Cynodon dactylon* allergens in 1997. In 1993 kikuyu grass, the first African grass pollen, was characterised in my unit at the University of Cape Town.

The second truly African grass to be characterised by Ruth Prescott, in our unit, was *Stenotaphrum secundatum* or buffalo grass to which 95% of grass-sensitive individuals have IgE antibodies as shown on immunoblotting. Further studies have also shown intense IgE responses to *Eragrostis curvula*, a grass very widespread in our region.

BOTANICAL RELATIONS OF GRASSES, SHOWING IMMUNOLOGICAL CROSS-REACTIONS

Of the tree allergens the predominant trees inducing allergy are oak and plane trees. Plane tree sensitisation was present in 15% of our athletes who participated in the Sydney 2000 Olympics. The African trees, e.g. acacia, doring boom appear to be weakly allergenic. Clinical observations by Dr Christo Buys (Windhoek) indicate that the prosopis tree of Namibia is highly allergenic.

Contact allergens are also present in our flora. The roots and leaves of the Zimbabwe creeper have been found to induce an intense acute allergic contact dermatitis in a study by Ruth Prescott.

Fungal spores too have caused severe allergies especially in asthmatics. The main fungal allergens include *Cladosporium alternaria* and *aspergillus* and a large cluster analysis of 2 094 subjects confirmed that a positive allergy response to cladosporium had an 83% predictive index for allergies to other fungal allergens in this cluster.

Our most recent work has addressed food allergens, occupational allergens and exotic African allergens. South Africa's coast is home to more than 10 000 species of marine fauna and flora representing about 15% of all coastal marine species worldwide. In a survey of 110 individuals in the Western Cape conducted by Karen Zinn, one of my dietetics honours students, we found a surprisingly high number of subjects, 35% of the study sample, who were allergic to molluscs.

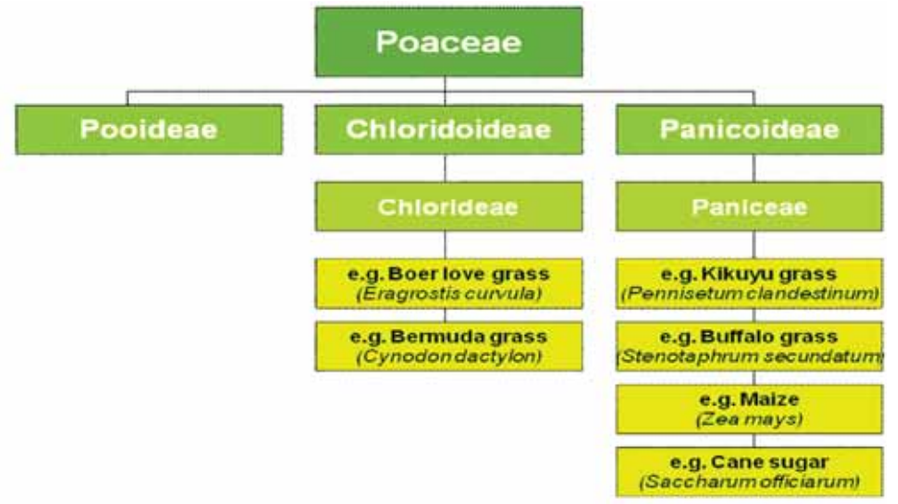
These studies led to the first reports of abalone hypersensitivity and the characterisation of the major allergen Hal m 1 by Andreas Lopata, a PhD student in my department. Production of a monoclonal antibody to this protein also led to the production of a forensic tool which can distinguish and trace the South African origin of canned abalone poached on our shores and ending up in the orient.

Mrs Bartha Fenemore.

Reports of the development of asthma in zoology students working with locusts at the University of Cape Town led to further laboratory studies by the group with Bartha Fenemore which confirmed the allergenicity of locust migration allergens and also identified new allergens of 70 kDa in the wings using Western blotting.

Other unusual allergens recently found to be of interest include cockroach allergens which appear to sensitise about 40% of polysensitised allergenic subjects and may be a risk factor for inner city asthma.

A recent study co-ordinated by Prof Mohamed Jeebhay in the Hex River Valley has also identified *Tetranychus urticae* to be an important allergen; 23% of the 207 workers studied in the vineyards had become sensitised to red spider mite compared with only 16% to house-dust mite.



The Poaceae family.

The most important new occupational allergy in South Africa emerged 10 years ago with the identification of latex allergy in health care workers who developed asthma, conjunctivitis, urticaria and even anaphylaxis in the work environment.

Having diagnosed the first case of latex allergy on the continent I embarked upon a survey of 2 000 health care workers of GSH and found the prevalence of latex allergy to be about 10%.

The Groote Schuur Hospital data was published and not only led to similar surveys at Red Cross (where the prevalence was found to be 6%) and Tygerberg (prevalence 18%), but has led to a new national policy document for health care workers banning the use of powdered gloves in South African hospitals, and respect for the rights and safety of health care workers in all hospitals and medical environments. Comprehensive studies of diagnostic nuances, effects of latex-free intervention and quality of life for health care workers have subsequently been conducted, with further studies on the proteomics and genomics of latex allergy being planned at the Centre for Proteomic & Genomic Research at the UCT Medical School (Institute of Infectious Disease and Molecular Medicine).

AN EXOTIC ALLERGEN

I was telephoned and asked to investigate the curator of the Johannesburg Snake Park who had developed severe asthma during public demonstration of the spitting cobra (rhinkals). He had never been bitten by a rhinkals cobra before.

With great effort Ruth Prescott managed to obtain the lyophilised cobra venom which when tested against the serum of the patient confirmed very strong specific IgE responses to 14 kDa phospholipases in the venom (and also present in phospholipases in venoms of mambas and diamond backed rattle snakes). We published the case in *Annals of Allergy*. This appears to be the first published case of sensitisation to a snake venom via the inhaled route.

CONCLUDING REMARKS

I have attempted to take you on a trip providing insight into why I decided to become an allergologist 20 years ago, rather than a cardiologist or a professional musician. Allergology in Africa is not only an important health priority affecting some 6.7 million South Africans, but Africa is a natural laboratory for studying the factors leading to the global epidemic of Allergy. In addition Africa has its own interesting and unique allergies which we have seen in our patients and been able to investigate in our laboratories.

In 1999 the Allergy Diagnostic and Clinical Research Unit opened at the UCT Lung Institute. It is the first of its kind on the African continent, and a state-of-the-art facility for diagnosis and management of allergic diseases. With a strong Allergy Society established 20 years ago, a popular Diploma in Allergy offered by the College of Medicine of South Africa and now recognition of allergy as a sub-speciality of medicine, family medicine and paediatrics by the HPCSA, about to be gazetted by the government, it is up to the government and the university to provide formal training posts for postgraduates and hopefully a chair of allergology to give allergology its rightful place, not only in the university, but the full recognition of allergology as the newest specialised discipline in medicine in South Africa.

THE FUTURE

1. The Position Paper of the World Allergy Organisation on Recommendations for Competency in Allergy Training for Undergraduates Qualifying as Medical Practitioners: Proper training of medical students in allergy is a priority for the future. Potter *et al*. *WAO Journal* 2009; 2: 150-154).
2. A formal postgraduate allergy training (MPhil) programme for specialists in medicine, paediatricians and family medicine is being processed through faculty structures of the University of Cape Town.
3. Negotiation is required with health planners to provide appropriate allergy diagnosis and treatment at primary, secondary and tertiary level around the RSA.
4 To continue to encourage and promote CME education in allergy and the work of the Allergy Society of South Africa and also with industry.
5. To promote and develop facilities for research into allergology issues specific and relevant to the African continent

ACKNOWLEDGEMENTS

Scientists: Dilys Berman, Ann Cadman, Corena de Beer, Bartha Fenemore, Pamela Lockey, Andreas Lopata, Barbara Nurse, Ann Orren, Ruth Prescott, Magda Schinkel. **Clinicians:** Nicola Brathwaite, Christo Buys, Gloria Davis, George du Toit, Matt Haus, Di Hawarden, Mohamed Jeebhay, Asmah Johar, Farouk Jooma, Sharon Kling, Ahmed Manjra, Cas Motala, Charlie Obihara, David Ordman, Sumaya Salie, Lorne Shore, Harris Steinman, Christo van Niekerk, Eugene Weinberg, Neil White, Heather Zar, Karen Zinn. **Nursing Staff:** Sheila Baker, Grace Poggenpoel, Heidi Thomas, Geraldine Brown, Yvette Crombie, Ann Toerien, Joan Meadows, Maria Ramsay. **Secretarial Assistance:** Ruwayda Adams, Angela Phillips, Lindi Terblanche, Estelle Berrill, Jacqui

Higgins, Jade Poggenpoel. The Allergy Society of South Africa, The University of Cape Town Lung Institute, Mr Jack Larsen, Mr Steve Lee.

REFERENCES

1. Adams J, Gie R, Potter PC, Beyers AD. Decline in total serum /IgE after treatment for tuberculosis. *Lancet* 1999, **453;** 2030-2033.
2. Obihara C, Beyers N, Potter PC, Kimpen J. The association of prolonged breastfeeding and allergic disease in poor urban children. *Eur Respir J* 2005; **25:** 970-977.
3. Steinman H, Dawson H, Kawalski M, Toerien A, Potter PC. Bronchial hyperresponsiveness and atopy in urban and rural South African children. *Paediatr Allergy Clin Immunol* 2003; **14:** 383-393.

Other references available on request.