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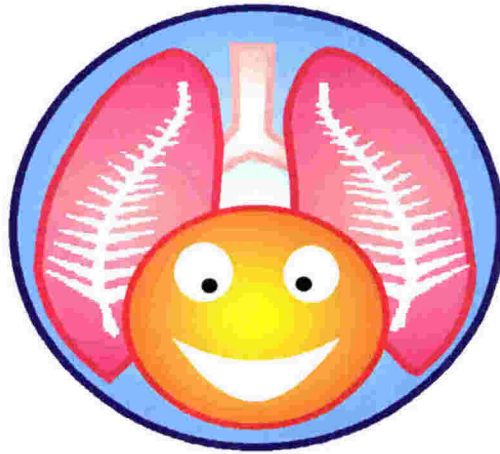
**PAEDIATRIC BRONCHIECTASIS IN AUCKLAND, NEW ZEALAND;
NON-INVASIVE SCREENING FOR CILIARY DYSFUNCTION AND AIRWAY INFLAMMATION.**

ELIZABETH ANNE EDWARDS

**DOCTOR OF PHILOSOPHY (PhD) IN PAEDIATRICS,
THE UNIVERSITY OF AUCKLAND, 2003**

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Park Road, Grafton
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RESEARCH LOGO



“Happy Healthy Kiwi Lungs”

ABSTRACT

Background: 'Bronchiectasis' is usually a progressive disease defined as bronchial dilatation, with or without associated bronchial wall and lung parenchymal damage, and classically with pus in the bronchial lumen. There is no knowledge on the prevalence, aetiology, and severity of paediatric bronchiectasis in New Zealand. Primary ciliary dyskinesia (PCD) is an inherited disorder that can cause bronchiectasis and is characterised by specific structural ciliary abnormalities leading to impaired ciliary motility. It has been suggested that ciliary abnormalities may predispose Maori and Pacific Island people to bronchiectasis, but appropriate expertise and non-invasive technology to accurately investigate the condition has not been available in New Zealand. Additionally the exhaled gas nitric oxide (NO), a non-invasive marker of some types of airway inflammation, has been suggested as a useful screening test for PCD. The aims of this thesis were to:

1. Define the demographics, causes, and severity of the known paediatric bronchiectasis population of Auckland.
2. Establish a method for detecting primary and secondary ciliary dysfunction.
3. Explore non-invasive methods for differentiating primary and secondary ciliary disease.
4. Determine the prevalence of PCD in paediatric bronchiectasis in Auckland.

Methods: Observations were made on children with bronchiectasis who attended the Starship Children's Hospital, and a cohort of healthy children recruited from local Auckland schools. A retrospective review of the demographics and radiology scores (CXR and HRCT scan) as a measure of disease severity was made. The results were compiled into a bronchiectasis database and a measure of socio-economic factors (NZDep96 index) was incorporated. Equipment was created for the photometric method of assessment of ciliary beat frequency (CBF). After piloting, 3 prospective studies were undertaken to evaluate skin prick allergy tests, exhaled and nasal NO, lung function and a nasal brushing for assessment of CBF and ultrastructural analysis in the normal and diseased children.

Results: The estimated prevalence of paediatric bronchiectasis in Auckland was ~2/10,000 and was disproportionately more common in the Pacific Island (6.3/10,000) and Maori children (2.8/10,000). Eighty eight percent of cases had bilateral disease, and 64% had 4 or more lobes involved. There was a wide range of presumed aetiologies but over half remained undiagnosed despite extensive investigation. The median duration of symptoms before diagnosis was 3.2 years, and a median of 4 respiratory admissions pre-diagnosis. The NZDep96 index suggested significant associated socio-economic deprivation. A non-invasive protocol to brush nasal epithelium and the technology to assess CBF was created and piloted. Ethnic normal values were established for NO and CBF for healthy European and Pacific Island children. Insufficient Maori children could be recruited. CBF and NO values were not low and comparable with frequencies reported internationally using similar methodologies. Exhaled NO levels did not differ significantly between the children with bronchiectasis and controls, or between the bronchiectatic children who were and were not prescribed inhaled steroids. However CBF and nasal NO were lower in the children with bronchiectasis than controls. The percentage of abnormal ciliary structural defects in the control children was 3 times higher than reported controls, with no difference across ethnic

groups. Similar abnormalities were seen in the children with bronchiectasis. These abnormalities were central microtubule defects, tubular additions or deletions, and partial dynein arm defects. In the individual children with bronchiectasis who had low CBF and nasal NO, no single primary ciliary defect was identified to conclusively diagnose PCD.

Conclusions: Paediatric bronchiectasis is common and severe in Auckland, New Zealand but the condition has been neglected in terms of recognition. It is hoped that the establishment of a bronchiectasis database for children will not only facilitate collaborative research but also act as a template for a national bronchiectasis database for New Zealand, which can be used to support applications for health resources and funding. Importantly the thesis has resulted in a non-invasive method for assessing ciliary structure and function that could be used to investigate New Zealand children and adults. A wide variety of ciliary abnormalities were found in the New Zealand children that were most likely secondary phenomena, and the incidence of PCD in the population examined, if present, is small. More work is needed to increase the ciliary structural and functional 'library' for New Zealand children, and particularly for Maori children who were under assessed in this work. The possibility of another vulnerability factor, as yet not identified, either of innate immunity or airway defences may still underlie the high prevalence of bronchiectasis in New Zealand.

ACKNOWLEDGEMENTS

Many experts have supported me through this work, but undoubtedly my principal supervisor Dr Catherine (Cass) Byrnes deserves major recognition and thanks. None of this work would have happened without her initiation and drive. Her 'let's make a list' optimism and enthusiasm throughout the long ride on the research roller-coaster, has been second to none. I know I have been very lucky to have such a supportive and approachable supervisor. I am proud to say that I was Dr Byrnes first research fellow, and hope that her exceptional mentoring skills will be fully recognised in the completion of this thesis.

I was also extremely fortunate to have Associate Professor Andrew Bush as my thesis and clinical supervisor while in the United Kingdom. The research and clinical experience gained at the Royal Brompton Hospital in London was invaluable. Dr Bush's thoroughness and attention to detail, combined with his patience and absolute backing to complete the job, was incredible.

All the members of the Starship Children's Hospital respiratory team have contributed significantly to this project. I would particularly like to mention Professor Innes Asher who gave valuable input into the original fellowship and grant applications that launched this research; Mrs Cathy Douglas and Mrs Shelly Broome, who gave considerable support with spirometry and NO analysis; and Mrs Sarah Butler who contributed important 'on-the-job' experience about the children with bronchiectasis, their compliance with chest physiotherapy, and with whom I compiled the information leaflets and bronchiectasis video for the families and schools.

This research project would not have happened without funding from a number of agencies – Glaxo Wellcome fellowship (salary for year 1), The Health Research Council Of New Zealand fellowship grant (salary for years 2-4), Starship Foundation (purchase of the microscope), Lottery Health Commission (research project grant), Asser Trust (research project grant), and Asthma Auckland (research equipment). In their spare time the technology and equipment to perform ciliary beat frequency measurements was made possible through the vision and energies of various Fisher & Paykel engineers particularly Mr Graeme Murray (Heated stage manufacture, Murray design, New Zealand), Mr Robin Williams (Photometer), Mr Matthew Payton (Computer software and graphics), and Mr Peter Hunt (Research logo).

A special thank-you to Dr Russell Metcalfe for his radiology tutoring and completion of the CT scores along with Dr David Milne. Mrs Metua Fa'asisila along with The Pacific Island Family Support Service and Kaitiaki (the Maori support services at Starship) gave invaluable cultural advice throughout this work. Their guidance and liaison with families as the project progressed contributed significantly to the projects success. I thank Dr Elizabeth Robinson and Dr John Thompson for their statistical advice and assistance. Associate Professor John Kolbe, and Mrs Wendy Ferguson shared information on adult bronchiectasis in Auckland, and allowed me access to use the NO analyser at Green Lane Hospital. Associate Professor Cynthia Jensen, Dr Charles

Anthony Poole, Ms Maureen Watson from the Department of Anatomy at the University of Auckland gave considerable time not only with submitting grant applications, but technical support in cilia ultrastructural analysis and light microscopy. I am especially grateful to Ms Ann Dewar from The Royal Brompton Hospital London for teaching me how to process and analyse cilia for the electron microscopy. Without Ann's input and energy no ultrastructural results would have been obtained. I thank Addressing Solutions Limited who compiled the New Zealand deprivation index maps without charge.

My thesis would not be complete without a huge thank you to all the children and young people who took part. I would also like to acknowledge the hard work and enthusiasm of the schoolteachers, who encouraged the students to volunteer and were flexible about them missing their lessons. The very special interaction with children and their families that this work has allowed is an experience I will cherish.

Finally I would like to dedicate this thesis to my husband and parents. My husband, Bryan Peterson, whose objective insight into the project, engineering and computer skills, unerring patience and love has supported me throughout all aspects of this work. I thank him also for his acceptance of the impact this work has had on both of our lives. Lastly I would like to acknowledge my Mum and Dad who bestowed on me not only a Liverpoolian sense of humour, a vital research tool, but the belief that with hard work I could realize my hopes and dreams.

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Figure 8.1. Proposed flow diagram for the investigation of suspected PCD in New Zealand.

LIST OF ABBREVIATIONS

| | |
|----------------------|--|
| ABPA | Allergic broncho-pulmonary aspergillosis |
| ALL | Acute lymphocytic leukaemia |
| AML | Acute myeloid leukaemia |
| ASD | Atrial septal defect |
| ASH | Action on Smoking and Health |
| ATP | Adenosine triphosphate |
| ATS | American Thoracic Society |
| CBF | Ciliary beat frequency |
| CF | Cystic fibrosis |
| CM | Clinical modification |
| cNOS | Constitutive nitric oxide synthase |
| C of V | Coefficient of variation |
| CSOM | Chronic suppurative otitis media |
| CT | Computed tomography |
| CXR | Chest radiograph |
| DHST | Delayed hypersensitivity skin tests |
| DOB | Date of birth |
| ENT | Ear, nose and throat |
| eNO | Exhaled nitric oxide |
| ERS | European Respiratory Society |
| FEF ₂₅₋₇₅ | Forced expiratory flow between 25-75% of the FVC |
| FEV ₁ | Forced expiratory volume in one second |
| FH | Family history |
| FRC | Functional residual capacity |
| FTT | Failure to thrive |
| FVC | Forced vital capacity |
| GORD | Gastroesophageal reflux disease |
| GP | General practitioner |
| HFA | Health Funding Authority |

| | |
|------------------|--|
| HRCT | High resolution computerised tomography |
| ICD | International classification of disease |
| IL | Interleukin |
| iNOS | Inducible nitric oxide synthase |
| ISAAC | International study of asthma and allergies in childhood |
| KS | Kolmogorov-Smirnov test |
| LIP | Lymphocytic interstitial pneumonia |
| LLL | Left lower lobe |
| LRTI | Lower respiratory tract infection |
| LUL | Left upper lobe |
| MMR | Measles, mumps, rubella |
| MRSA | Methicillin resistant Staphylococcus aureus |
| MTT | Mucociliary transit time |
| NBT | Nitroblue tetrazolium |
| NF- κ B | Nuclear factor kappa B |
| NHI | National Health Index |
| nNO | Nasal nitric oxide |
| NO | Nitric oxide |
| nNOS | Neuronal nitric oxide synthase |
| NZDep96 | New Zealand deprivation index 1996 |
| PCD | Primary ciliary dyskinesia |
| PCR | Polymerase chain reaction |
| PDA | Patent ductus arteriosus |
| RLL | Right lower lobe |
| RML | Right middle lobe |
| ROC | Receiver operator curve |
| RSV | Respiratory syncytial virus |
| RUL | Right upper lobe |
| SaO ₂ | Arterial oxygen saturation |
| SD | Standard deviation |
| TLC | Total lung capacity |
| TNF | Tumour necrosis factor |
| URTI | Upper respiratory tract infection |
| VC | Vital capacity |
| VSD | Ventricular septal defect |
| WHO | World Health Organisation |