

Mucosal immunization for bacterial respiratory infections

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Published

2008

Journal Title

Human Vaccines

DOI

[10.4161/hv.4.6.7057](https://doi.org/10.4161/hv.4.6.7057)

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Portrait – Human Vaccines – ALLAN CRIPPS

The loss of millions of children each year to vaccine preventable diseases is a statistic which haunts me. Best estimates are that 2.5 million children under the age of five die each year from pneumonia. When I have the opportunity to present our research at both national and international conferences and when lecturing to students I show an image of a Boeing 747 aircraft and ask “.....*is it acceptable to you that an aircraft such as this leaves your local airport, fully laden with small children less than five years of age approximately every hour and never returns? This is equivalent to the global impact of vaccine preventable pneumonia*”.

The morbidity figures for respiratory infections are even more staggering. About 150 million new cases of pneumonia in young children occur every year in developing countries. Middle ear infections are the most common childhood illness with tens of millions of children affected by this disease and many suffering hearing loss as a result. While otitis media affects virtually every child on the planet, those most at risk are the children of developing countries and those within Indigenous nations of advanced western countries such as Australia. Many of these children will never reach their full potential due to the serious sequelae of otitis media. The sad reality of this situation is that we have the vaccines available and the know-how to rapidly develop new

vaccines to significantly reduce the mortality and morbidity of childhood respiratory infections.

My first exposure to the overwhelming burden of childhood respiratory infections came on a trip to the highlands of Papua New Guinea in the late 1970's. I was visiting the PNG Institute of Medical Research, then directed by Dr Michael Alpers, to participate in a malaria serology study and to design a study of mucosal immune competence in children whose upper airways are endemically colonised with very high bacterial loads within weeks of birth. I was galvanised by a ward round at Goroka Base Hospital where there were a number of children with severe pneumonia and little hope of survival despite the excellent care that the hospital provided. Many of these children presented to hospital too late for effective intervention. As part of the research, I also visited highland villages where the extent of respiratory disease in the adult population was clearly evident. When I returned to Australia my research became focussed on characterising the human mucosal immune system and the development of mucosal immunisation strategies for bacterial respiratory infections.

My own childhood was one of amazing freedom. I was born into a farming family. My mother's family had been pioneers in Australia's Northern Territory but their property was lost in the Great Depression. Her father worked as a farm labourer and she had to move away from home to train as a nurse. She graduated as dux of her class. My father's family had small land

holdings in northern New South Wales and he often supplemented the family's farm income by droving sheep. I have fond memories of "helping" him in the woolshed at shearing time and watching him adjust red hot iron shoes so that they fitted each of the horse's hooves. Later in his life he became quite a successful small businessman operating a convenience store on the outskirts of town. Growing up in rural New South Wales, my early education was provided by Blackfriars Correspondence School and supervised by my mother. We moved off the farm when I was about nine years of age and I had a few short years in the small, three-teacher, Westdale Primary School, before more change. For a boy from the bush who had enjoyed such a free and unstructured early childhood, the transition to a secondary boarding school was something of a challenge. From an academic perspective however, the supervised learning at Farrer Memorial Agricultural High School was probably the best thing for me. When I arrived at the School I was not a very confident child which no doubt reflected my relatively isolated early years. However, through the efforts of some very dedicated teachers my confidence and self esteem grew. I loved being out in the bush so the weekend geology excursions were a highlight during those years. It was the beginning of my enjoyment of science and the process of enquiry.

There have been a couple of turning points in my life when I considered becoming either a veterinary surgeon or a medical doctor but as a teenager who had only visited Sydney two or three times, the idea of moving to such a

large city to study was just too daunting. With the support of my parents and an Australian Commonwealth Scholarship, I chose to study at the University of New England (UNE) in Armidale some 80 miles from my home. During my undergraduate and postgraduate studies I worked odd farm jobs, including mustering cattle on the southern highlands of New South Wales in the summer vacations. I was the first member of my extended family to complete high school let alone undertake University studies. What to study was an interesting dilemma. I finally settled on a science degree with a major in physiology and supporting courses in anatomy, microbiology and biochemistry. I was greatly influenced in this choice by Professor Jack Evans, the Foundation Professor of Physiology at UNE and my Honours supervisor Associate Professor Vernon Williams who both wisely persuaded me that such a program of study would be an excellent basis for a career in medicine, veterinary science or research. I graduated from UNE with First Class Honours in Physiology and a publication in the *British Journal of Nutrition* on the function of the small intestine during pregnancy and lactation. Fate was to again intervene and I was awarded a second Commonwealth Scholarship to undertake a doctoral program of research. Vernon convinced me that I should take up this scholarship at the University of Sydney where he had a colleague, Professor Alick Lascelles, who he thought would be a good mentor for the shy bush kid. I followed his advice and travelled the 300 miles to Sydney. My summer holiday assignment was to read the entire volume of *Yoffey and*

Courtice: Lymphatics, lymph and the lymphomyeloid complex. Sure enough, at my first meeting with Lascelles he asked if I had read the text. Luckily I had, as it was essential for the research program that I was about to undertake.

Lascelles, a veterinarian, had undertaken his PhD with Professor Bede Morris at the John Curtin School of Medical Research at the Australian National University. Morris and Lascelles developed the surgical techniques that enabled the long term cannulation of both efferent and afferent lymphatics in conscious sheep. They were particularly interested in the barriers that separated blood, interstitial fluid and the lymph. My PhD was to study the origin of immunoglobulin in mucosal secretions using the whole animal physiological approach for which Morris has now become legendary. My training in experimental physiological surgery at UNE held me in good stead. I also became highly proficient in a whole range of protein purification procedures and the establishment of in-house immunoassays in an animal model for which there were no commercial reagents. At the time when the function of human secretory IgA was being unravelled by Pearay Orgra and others, my task was to purify ovine secretory IgA for the first time. It took six months and the experience was invaluable in developing animal models of human respiratory infections later in my career. My PhD studies set a career course in mucosal immunology. By the mid 1970's we had demonstrated that virtually all IgA present in saliva, intestinal secretions and milk was produced locally at the mucosal site. There was also some local production of the IgG1

subclass in the sub maxillary salivary gland. In addition, local responses to intestinal parasitism were characterised and differences in responses documented between infected and non-infected isolated loops of intestine in-situ. This is some of the first evidence to support the concept of localised mucosal immune networks and the findings were supportive of the common mucosal immune system being hypothesised by Professor John Bienenstock, Dr Robert Clancy and colleagues at McMaster University in Canada around the same time.

On completing my doctoral studies I had the research bug. However, I was not through with my flirtation of the possibility of a career in medicine. So I declined a post-doctoral position continuing animal based immunological research with Bede Morris in Canberra and took up a job as a hospital scientist in the Department of Clinical Immunology at Flinders Medical Centre in Adelaide, South Australia. I'm not certain that Bede ever forgave me as he indicated that I had "gone to the dark side". It is strange that these words were only repeated a couple of years ago by noble laureate Peter Doherty when he learnt that I had taken a leading administrative role with my current university. The move to Adelaide was fortuitous. I met Dr Andrew Kemp, an academic clinician, and we collected and analysed immunoglobulin levels in repeated salivary samples of three infants from birth. This was the beginning of a major study on the ontogeny of the human mucosal immune system.

In 1978 I met up with Professor Robert Clancy at a conference. Clancy had recently returned to Australia from Canada and been appointed as the Foundation Professor of Pathology at the new Medical School at the University of Newcastle. I had now made the decision to develop a career path as a biomedical scientist and in 1979 took up a position to work with Clancy as the Scientific Director of the regional diagnostic immunology laboratory and to develop a mucosal immunology research unit. This was the commencement of a lengthy successful collaboration and highlights the benefits of collaboration between academic clinicians and biomedical scientists. Since this time I have balanced a research career with senior administrative roles in either the health service or universities.

The 1980's were a fantastic time for the Newcastle research team. The new medical school, based on the Canadian McMaster model, was young and vibrant and the construction of a new teaching hospital filled us all with enthusiasm. With PhD student Maree Gleeson, we continued the work I had begun with Dr Andrew Kemp in Adelaide and undertook the most comprehensive longitudinal study ever conducted on the development of mucosal immunity in infants and children. The impact and application of this work is now being realised as we grapple with the development of mucosal vaccines to control respiratory infections caused by commensal bacteria of the nasopharynx where sterilising immunity may not be desirable. We hypothesised that the mucosal immune response, particularly IgA, was critical

in the prevention of bacteria descending from the nasopharynx into the lower airways causing pneumonia or acute exacerbation of chronic bronchitis. We further hypothesised that stimulation of mucosal responses by oral immunisation would provide the best defence against lower respiratory tract infections by controlling the bacterial load of the upper airways. Animal models relevant to human infections were established for non-typable *Haemophilus influenzae* (NTHi) and *Pseudomonas aeruginosa* and a large volume of pre-clinical data that supported our hypotheses was generated. Immune parameters in the animal models that appeared to be important in protection included specific IgA antibody, CD4⁺ T cells and the polymorph response to the lung. Studies then progressed to human trials of a whole killed cell NTHi vaccine in Australia and the PNG highlands - most of which demonstrated a positive clinical outcome. Again stimulation of a T cell response appeared to be important in the acquired protective response. Studies on children in PNG led us to hypothesise that early bacterial colonisation of the airways with high levels of bacterial load results in a hypo-responsiveness in the mucosal immune responses. Data from a number of our studies since then have supported this position. With graduate student Diana Taylor, we were also able to demonstrate the importance of humoral innate immunity in respiratory defence. In patients with chronic lung disease we observed that their susceptibility to respiratory infection was related to the level of the

antimicrobial protein, lysozyme, in mucosal secretions. A decade later we revisited this in elite athletes who are also susceptible to respiratory illness.

With the increasing demands of clinical diagnostic work it became difficult for me to maintain my research activity and in 1996 I accepted a position as Dean of Applied Science and Professor of Health Sciences at the University of Canberra. Dr Jennelle Kyd who had undertaken a PhD program with me in Newcastle also moved to Canberra as a Research Fellow to help me establish what was to become known as the Canberra Centre for Mucosal Immunology. For almost a decade, I continued the work with Dr Kyd and a number of graduate students on the development of bacterial respiratory vaccines by identifying potential vaccine antigens for NTHi, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *P. aeruginosa*. With graduate student Ruth Foxwell, we demonstrated the importance of macrophages and CD8+ T cells in the early stages of the acquired immune response in the lung. We developed new animal models that allowed us to study otitis media including polymicrobial infections and chronic lung infections. Wonderful international collaborations and enduring friendships followed from our work and the international travel that is necessary for us, as Australians, to keep at the forefront of research.

Two further major ontogeny studies in children have been undertaken and we are still in the process of analysing this data. The first study examined the impact of pre-school on the ontogeny profile and the second with Dr Deborah

Lehmann and the Kalgoorlie Otitis Media Research Project team from the Institute of Child Health in Perth has examined the association of mucosal immune competence and bacterial colonisation to otitis media in indigenous and non-indigenous children. Being located in Canberra presented a unique opportunity to study the mucosal immune function of elite athletes training at the Australian Institute of Sport (AIS) who often present with respiratory like illness most probably as a result of overtraining stress. This work continues some two decades since the research team of Professors David Pyne, Maree Gleeson, Peter Fricker, Robert Clancy, Dr Peggy Horn and I first started working together. Collectively we have demonstrated that intense exercise compromises mucosal immune function, both innate and acquired, and increases the risk of upper airway symptoms and infections. With graduate student Nicholas West, we are currently examining the efficacy and effectiveness of “immuno-modulating” nutrition supplements to ameliorate exercise induced immune perturbations, particularly humoral innate immunity, in elite athletes at the AIS facilities in Canberra. If successful, the findings of these studies will be applicable to the broader community, where stress-induced immune compromise is proposed to underpin a range of illnesses and chronic disease.

In 2003 I relocated to Griffith University to establish a new medical school at the University’s Gold Coast campus. In 2005 the University merged its 10 health related schools into a single faculty structure and appointed me as the

Executive Head. The group is one of Australia's largest health faculties with over 5,000 full time students. Despite this administrative load I remain committed to my discipline of mucosal immunology and the children of the world to whom respiratory infections are a threat to survival. The major barrier for effective oral immunisation is the efficient antigen targeting of M cells of the Peyer's patches in the intestine. Studies we undertook in Canberra with graduate student Peter Tyrer demonstrated that specific common microbial pathogen-associated molecular patterns are recognised by pattern recognition receptors on the surface of the M-cells and this interaction initiates the transcytosis of particulate antigen through the M-cell to antigen presenting cells on the basolateral surface. Research currently being conducted at Griffith University aims to further understand this innate receptor system and determine whether or not it can be exploited for practical vaccine delivery.

In recent years I have devoted considerable time to leadership of both the mucosal immunology discipline and to vaccinology. I co-chaired with the late Professor Graham Jackson, the 9th International Congress of Mucosal Immunology in Sydney; established and chaired the Australasian Society for Immunology Special Interest Group in Mucosal Immunology; been an active participant of the World Congresses on Vaccines, Immunisation and Immunotherapy and International Symposia on Otitis Media; and co-chaired with Amanda Leach, the 5th International Symposium on Pneumococci and

Pneumococcal Disease (ISPPD-5) in Alice Springs. I am proud that the major outcome of ISSPD-5 was the ISPPD Declaration – a Global Action Plan against childhood pneumonia. This represents a commitment from a significant body of world clinical and scientific researchers to address the appalling loss of life, particularly of children, caused by pneumonia. The challenge will be whether or not the international community has the will to push for funding and implement the much needed interventions including vaccination, case management, and a reduction of risk factors such as poor nutrition, indoor pollution and HIV infection.

I have had a privileged career. I was encouraged by my parents to succeed. I have been supported by wonderful and talented people. It has been my honour to supervise over 30 graduate students who have contributed substantially to the research outcomes. Working with these enthusiastic and brilliant young minds has kept me passionate about discovery and gives me great hope for the future. Our research has been characterised by a comprehensive and physiological approach. Research into the most basic aspects of mucosal immune function has been streamed alongside relevant animal models and applied human research wherever possible.

“We are made wise not by recollection of our past, but by the responsibility for our future.”- George Bernard Shaw