

TVW Telethon Institute for Child Health Research



Annual Report 2000

Affiliated with
The University of Western Australia
and Princess Margaret Hospital for Children

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Mission

To improve the health of children through the development and application of research into the causes and prevention of ill-health and the maintenance of health

Aims of the Institute

- to conduct high quality research
- to apply research findings to improve the health of children, adolescents and families
- to teach the next generation of health researchers
- to be an advocate for research and for children

Early Origins of Childhood Disease: Research Programs at The TVW Telethon Institute for Child Health Research

- Aboriginal Health
- Asthma and Allergies
- Birth Defects
- Biostatistical Methods
- Childhood Disabilities and Death
- Child and Adolescent Mental Health
- Infectious Diseases
- Leukaemia and Cancer Research
- Perinatal Epidemiology

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Chairman's Report

Kevin Campbell AM



In many ways the year 2000 marked the coming of age for the TVW Telethon Institute for Child Health Research. This was symbolised in the celebrations surrounding the official opening of the new building by the Governor General, His Excellency Sir William Deane AC, KBE, on 1 September 2000. Symbolic too from a national perspective was the launch of the Kulunga Network, the Institute's centre for indigenous child health research, as a curtain raiser to the official opening.

Year 2000 will also be remembered as the year of the Sydney Olympics. As a nation, Australia revelled in the success of our sporting heroes, including the Para Olympians. Perhaps less obvious but equally as significant, the Institute was able to herald during the opening ceremony some outstanding national heroes in science and medical research. These included: Nobel Laureate, Professor Peter Doherty and the Chairman of the Health and Medical Research Strategic Review Committee, Mr Peter Wills AM. While unable to be there, elder statesman of Australian medical research and champion of the cause for national reconciliation, Professor Emeritus, Sir Gustav Nossal AC was part of the occasion nevertheless. These champions along with those of our own in Western Australia exemplified by our Director, Professor Fiona Stanley AC and her team of outstanding senior researchers, are inspirational to the nation.

This Institute has robust and enduring research output. The measures of excellence in 2000 included nearly \$4 million being awarded for peer reviewed national competitive grants including NHMRC grants; close to 100 recognised research publications; and the joint supervision of 40 or more postgraduate students. In addition commercial and government research contracts attracted a further \$3.5 million. This is an outstanding achievement for a research institute that has been in operation for just over 10 years.

The move to the new building in March was the culmination of years of grant seeking, fundraising, consultation and dedicated planning by our Director, Professor Fiona Stanley and her staff, the Board of the Institute and the many donors and supporters. We remain indebted to the Commonwealth Government and the State Government for their combined investment in the long-term interests of child health research in Western Australia through the building grant of \$22.5 million.

We recognise too that the example had been set earlier by the business community and the broader community in their generous support for the "Give Every Child A Chance Campaign". Through the pledged support of Telethon, Australian Capital Equity, Wesfarmers, and over 200 Australian based business houses and private donors, by Year

2000 over \$10 million of the pledged \$11.8 million for a campaign of 5 years had been received. Most of the remaining pledges will be honoured in 2001.

On behalf of the Board I would like to thank the raft of volunteers who support the many not for profit, non government charitable organisations dedicated to raising funds for research into the many diseases that afflict our children.

I would like to single out the Variety Club of Western Australia. As a community based charitable organisation which raises funds solely for the benefit of children, the Variety Club has during the last decade, raised nearly a million dollars in support of child health research, through the sponsorship of the Director's professorial Chair.

I would like to thank our long standing auditors, KPMG, who for many years have provided for us an outstanding service and have been great supporters of the work of the Institute. I wish to acknowledge work undertaken for the Institute by solicitors Clayton Utz and also Freehills.

Finally may I once again pay tribute to the members of the Board of the Institute. The long-standing members, Professor Lou Landau AO and Mr Harvey Coates continue to provide leadership and vision. I was pleased during 2000 to welcome new members to the Board and these appointments were ratified at the Annual General Meeting in May. They were: Mr Keith Jones, Managing Partner of Deloitte; Ms Rebecca Maslen-Stannage, Partner at Freehills; and Mr Michael Daube, Chief Executive Officer of the Cancer Foundation. I am also grateful that Dr Graham Mitchell AO, Chief Scientist of Victoria, was able to participate at Board meetings via teleconference, and has now accepted a formal position on the Board. During the year too, we farewelled Mrs Rae Willis as President of the Friends, and I was able to welcome the incoming President, Mrs Marilyn Stewart, as a member of the Board ex officio.

Each of the Board members is actively involved in the Board committees which play such an important role in the governance of the Institute. I am proud to be associated with such outstanding professional people who devote so much of their time to the benefit of the Institute, and who share a vision of healthy children and a healthy community. As a Board we are proud that we have been able to contribute to the coming of age, and we look forward to the growth and development of the Institute and its people in the twenty first century.

Kevin Campbell AM

Board of Directors



Mr Kevin Campbell AM

Chairman, TVW Telethon Institute for Child Health Research;



Mr Harvey Coates

MBBS MS Diplomate American Board Otolaryngology FRACS FACS FRCS(C) Senior Ear, Nose and Throat Surgeon, Princess Margaret Hospital for Children.



Mr Mike Daube

BA(Hons), Hon. D. Sci (Curtin) Chief Executive Officer, Cancer Foundation of Western Australia



Mr Keith Jones

BBus, A.C.A., CPA, Board Member, Deloitte Corporate Finance Pty Ltd Managing Partner, Deloitte Touche Tohmatsu Western Australia



Professor Louis Landau AO

MD FRACP Dean, Faculty of Medicine and Dentistry, The University of Western Australia.



Ms Rebecca Maslen-Stannage

LLB (Hons) BComBCL (Oxon) Partner, Freehill Hollingdale & Page



Dr Graham Mitchell AO

RDA, BvSc, FA CVSc, PhD, FTSE, FAA Principal, Foursight Associates Pty Ltd



Professor Fiona Stanley AC

MD MSC FFPHM FAFPHM MFCCH FRACP(Hon) FRACOG Scientific Director of the TVW Telethon Institute for Child Health Research; Professor, Department of Paediatrics, The University of Western Australia; Member, Prime Minister's Science, Engineering and Innovation Council.



Mrs Marilyn Stewart

President, Friends of the Institute

Committees of the Board in 2000

The Board of Directors manages the overall business of the Institute and meets six times during the year. In order to carry out business effectively, the Board is supported by various committees which offer advice in specific areas.

Building Committee

Mr Michael Lewis (Chairman)
Mr Garry Lawrence
Mr Bill Wright
Mr Bruce McHarrie
Mr Robert Ginbey
Mr Nino Gullotti
Dr Thierry Venaille

Building Artworks Committee

Mr Harvey Coates (Chairman)
Sir James Cruthers
Ms Tammy Gibbs
Mr Robert Ginbey
Professor Fiona Stanley AC

Capital Fund Committee

Mr Kevin Campbell AM (Chairman)
Mr Harvey Coates
Prof Fiona Stanley AC
Mr David Berinson
Mr Bryce Denison (Wesfarmers)
Mr William Rayner (Telethon Trustees)
Mr Fred Stone (Australian Capital Equity)
Mr Michael Matthews (Plan B)
Mr Bruce McHarrie
Mr Robert Ginbey
Mr Nino Gullotti

Finance Committee

Mr Keith Jones (Chairman)
Mr Kevin Campbell AM
Prof Fiona Stanley AC
Mr Bruce McHarrie
Mr Robert Ginbey
Mr Nino Gullotti
Mr Kim Law

Scientific Advisory Committee

Prof Lou Landau AO (Chairman)
Prof Fiona Stanley AC
Prof Colin Binns
Mr Harvey Coates
Dr Cathy Cole
Prof Wayne Thomas
Prof Peter LeSouef
Dr Richard Loh
Dr Susan Prescott
Assoc Prof Richard Prince
Prof Geoff Stewart
Prof Charles Watson
Mr Bruce McHarrie

Fundraising Committee

Ms Rebecca Maslen-Stannage (Chair)
Mr Harvey Coates
Mr Michael Daube
Mr Bruce McHarrie
Ms Naomi Mellish

Appointments and Promotions Committee

Mr Michael Daube (Chairman)
Mr Bruce McHarrie
Prof Fiona Stanley AC
Prof Peter Sly
Prof Wayne Thomas
Prof Steve Zubrick

Director's Report

Fiona Stanley



In 2000, the TVW Telethon Institute for Child Health Research (ICHR) was 10 years old. The move to the new building was symbolic of our success so far; external evidence of the hard work and commitment needed to establish a centre of excellence in Western Australia (WA). Being in our new facility, provides an opportunity to look back at what has been achieved and of greater importance, to think carefully about where we want to go in the next 10 years.

When ICHR commenced in 1990, WA had little capacity to support new centres of excellence in health and medical research. Now we have a dedicated Medical & Health Research Infrastructure Fund (MHRIF), a Lotteries Health and Medical Research Committee and 4 Medical Institutes who have achieved National Health & Medical Research Council (NHMRC) or Association of Australian Medical Research Institutes (AAMRI) membership status. The status of health and medical research has changed and our Institute has been an important part of that process.

The year 2000 felt to me like a sea change for health research nationally and locally, and for ICHR specifically, for several reasons. All of us in Australian research were excited about the success of the (Wills) Review of Health and Medical Research Funding in Australia. I had the privilege of being a member of the implementation committee and participated in discussions about monitoring the impact of the review's recommendations, establishing Research Australia (to improve the knowledge and image of Australian medical science in the community), how best to encourage priority driven (including public health) research and its use to improve health status and medical care, and the challenges to commercialisation of Australian research. The Prime Minister's Science, Engineering and Innovation Council, on which I also serve, was discussing a significant Innovation package with the aim of increasing Australia's commitment to Research and Development (R&D), impacting positively on our capacity to do good science and to develop it here. Part of this package includes infrastructure funding, which would enhance our competitiveness for peer reviewed grants. The mechanism for allocation of this infrastructure, and whether independent Institutes like this one will be eligible, is still being decided. As you can imagine, we are trying hard to ensure success.

The local State scene was also promising with the formation of an Alliance of Research Institutes. The Lotteries Commission encouraged and facilitated this by continuing to provide a budget for facilities and equipment, but on the proviso that we collectively decided on what was best for all WA researchers. At the launch of the new gene array facility, an excellent symposium was held with national and local speakers. This gave us all a sense of WA really being there with the best of them! The Alliance will work together to increase WA's capacity in scientific research and will facilitate the development of a WA industry around it to ensure the benefits are realised locally as well as elsewhere. ICHR is one of the major players in these activities.

As an Institute we have also participated in effective negotiations for the establishment of a statewide Women's and Children's Health Authority, and cemented a business plan with the Health Department of Western Australia. This could see the Institute becoming the R&D arm of the Authority, providing both evidence of effective care and the capacity to monitor and evaluate indicators of success. Further discussions with Princess Margaret Hospital for Children and community and public health partners will ensure we have the best statewide service for families and children. Discussions with PMH and Telethon are continuing to ensure that we avoid competing for fundraising with the PMH Foundation.

Successful negotiations have also been conducted with the universities; with The University of Western Australia to set up the Centre for Child Health Research in the Faculty of Medicine and Dentistry and with Curtin University of Technology to set up a Centre for Human Development in the Faculty of Health Sciences.

The Institute's scientific program has already benefited from the move to the new facility. Our national profile of research success is now better than ever and we are considered leaders in a range of research areas such as asthma/allergy, psychosocial morbidity, developmental disorders and Indigenous health research. There is also a perception that our approach of being multi-disciplinary and our commitment to applying research results are well ahead of any other groups in Australia. I still think we have a long way to go! We were encouraged by the words of our Australian of the Year, Professor Sir Gustav Nossal AC, on his visit to the new building, "...this Institute is now exquisitely poised to capitalise on the new knowledge from the human genome, with its population data bases and multi-disciplinary capacity".

The year 2000 also saw the 21 year anniversary of our world renowned Cerebral Palsy Register and the publication of our monograph (Stanley, Blair and Alberman, 2000). The hard work and outstanding commitment of both Dr Eve Blair and Ms Linda Watson must be fully acknowledged here. Linda started the Register in 1977 and Eve has worked on the data since 1980. We celebrated 20 years of the Birth Defects Registry with an international symposium which showcased the Registry's output and influence; it was the first symposium in the new building. On 31st August, we launched the Kulunga network, a novel partnership between ICHR and all the Indigenous WA Community Controlled Health Organisations (WACCHO) to conduct relevant research, train and inform Indigenous researchers and communities, and make research work for communities by engaging Indigenous researchers. We are honoured that our Governor General, Sir William Deane AC, KBE agreed to be Patron in Chief and Professor Lowitja O'Donohue AC and Cathy Freeman are Patrons. And in May, after years of planning, we commenced the major field work for the Aboriginal Child Health Survey. The survey aims to collect unique data on 4500 families with children aged 0-17 years, across the State; and to obtain accurate estimations of morbidity including mental health and school problems and their protective and risk factors. This will inform policy and community actions to improve child and youth outcomes in health and well being.

A fascinating and potentially very important finding from a WA study of childhood leukaemia (Thompson, Armstrong, Fitzgerald & Willoughby, under review for publication), prompted us to form a national group to conduct a multi-centre case-control study Australia wide and coordinated by ICHR. The WA Cancer Foundation funded a one-day workshop in Perth in November to review the evidence and design the study, prior to writing the grant application. They have also agreed to fund a Research Officer for 3 years to coordinate the study. Any evidence leading to possible prevention of leukaemia in children is of enormous importance as, whilst survival rates have improved with better treatments, they are costly and damaging to the child and family.

The cancer research being conducted by Professor Ursula Kees and her group is working on more effective and less toxic cancer treatments. Knowledge of the genetic differences between cancer cells and normal cells can help identify novel diagnostic and therapeutic approaches. Major programs in oncogenesis, tumour suppressor genes, including those in brain tumours, are continuing. The brain tumour work is funded by the Three Boys Legacy.

In addition to Leukaemia, research into the causes of asthma and allergy continue to form the major plank of the research base in Laboratory and Clinical Sciences. The Year 2000 witnessed the start of a range of new initiatives in these areas, as well as consolidation of research efforts in some of our most longstanding and productive programs. Important new information has been obtained on the role of recently discovered aeroallergens in asthma, on the importance of Dendritic Cell populations in the airway wall in the early phase of asthma attacks in adults, and on the unique ways that the infant immune system responds to vaccines. We are also close to understanding how the functions of the immune system in the developing fetus are tightly controlled to prevent it from damaging the placenta, upon which it depends for survival, and we are confident that in the long term this particular research may unlock some of the secrets of how abnormalities such as Neural Tube Defects are initiated during fetal life. We have also been fortunate in attracting CJ Martin Fellow, Dr Cathy Jones, to a joint appointment at the Institute and the Department of Paediatrics, UWA, to extend our research on perinatal immune responses. Dr Jones who has studied the development of preterm responses to allergens and fetal cytokine production at the University of Southampton is adding expertise to our studies on perinatal immunology.

The Institute has grown in size and complexity over the last few years, justifying our demands for a new facility. By the end of 2000 we had 220 staff and students, not including all the field interviewers working all over WA for the Aboriginal child health survey. We are thinking carefully about future recruitment, to ensure we increase our existing strengths and expand only in those areas of most strategic importance for our future work. The aim is to add depth rather than more breadth. Dr Anne Read will retire in 2001 (our first retirement amongst our senior staff!) after 20 years of outstanding research and commitment to epidemiology and Indigenous health. Her replacement is crucial, not only for the research, but as a mentor and teacher for the Indigenous health research team. Dr Natalia Bilyk, my Executive Assistant over the last 5 years has been accepted into Flinders Medical School for 2001. She, too, has made an outstanding contribution to ICHR and has ensured that my work is of high quality. Her farewell speech to the Population Science Away Days in November brought the house down – both will be sadly missed by all of us.

The challenges facing our Institute and others committed to improving child and youth health and

well being are enormous. Over the last 30 years, we appear to have created what are being called “toxic societies”, which are having detrimental effects on a variety of outcomes for children, families and society generally.

We are observing epidemics of mental health problems (such as suicides, risk taking behaviours, ADHD, depression, eating disorders), of asthma and other complex diseases (preterm births and low birth weight, diabetes, inflammatory bowel disease, autism, cerebral palsy). In fact there are few conditions for which I can report a significant fall in incidence (neural tube defects, vaccine preventable infections and cot deaths in Caucasian but not in Indigenous children) (Stanley 2001).

Those in other research disciplines such as education and the social sciences are observing similar increases in developmental problems in children and young people (behavioural problems, learning disabilities, school drop-out) and in juvenile crime.

Neither our research nor our policy agendas have responded well to this crisis and as a society we simplify the solutions in a way that encourages expenditure where it will have least impact. Our epidemiological and basic biomedical studies, (even in our multi-disciplinary Institute), are limited in their capacity to elucidate the extremely complex causal paths to these problems. Some evidence suggests a commonality of pathways to these health, educational, psychosocial and criminal problems, suggesting that if the earlier factors in the pathways were known, then major preventive strategies early on could be effective for a range of outcomes, not just health.

On the whole very little of family and children’s policy in Australia in health, education or welfare is based on solid Australian research aimed at effective, long-term prevention.

It is obvious that we need an Australia wide research and policy agenda in response to this crisis in developmental health and well being, similar to our brilliant national campaign for the HIV/AIDS crisis in the 1980s.

We are a small country, in terms of population and critical mass of researchers. We all have databases, cohort studies and surveys, many of which have been funded by NH&MRC (health) or the Australian Research Council (ARC) (psychosocial, educational, crime). These could all be better utilised to inform the broader picture.

The next important phase for this Institute involves our participation in this national agenda. We must do so by ensuring our work is of the highest calibre and by making rigorous science work to improve health and well being for children, families and youth. We will need the help and support of this wonderful WA community more than we ever have before.

I would like to acknowledge and thank the Board, the Executive, Administration and all staff in ICHR for their fantastic work in 2000.

Fiona Stanley

References

Stanley FJ, Blair E and Alberman ED. The Cerebral Palsies: Epidemiology and Causal Pathways. London: McKeith Press (Cambridge University Press); 2000.

Stanley FJ. Centenary Article – Child health since Federation. In: 2001 Year Book Australia. Canberra: Australian Bureau of Statistics, ABS catalogue No. 1301.0, pages 368-400.

Chief Financial Officer's Report

Mr Bruce McHarrie



The achievements for 2000 and the initiatives put in place for 2001 and beyond are almost too many to identify, however, for the purposes of this report, I will touch on some of the key highlights.

Throughout the year there has been much publicity about the Institute's new research facility, reflecting the enormity of the project, the effort involved in rehousing a highly specialised activity and the overall success of having done so. It also reflects the achievements of the Institute as a whole over the ten years since its inception and we are now able to look forward to the challenges of next decade with confidence.

Those challenges will, of course, include dealing with the financial implications of supporting an organisation of this type and it was encouraging to see the State Government's move to double the Medical Health Research Infrastructure Fund (MHRIF) during 2000, to take effect at the end of 2001.

Medical research organisations are complex and the MHRIF funding, significant as it is, falls well short of that required to provide the necessary support. Consequently we are very reliant on a number of other funding sources such as our affiliation with the University of Western Australia and a variety of fundraising activities coordinated by our Development Office. Government lobbying will therefore continue to be a feature on our landscape as we continue to raise awareness of the importance of the medical research industry in Western Australia.

To that end, the Institute is a member of the Biomedical R&D Alliance. This Alliance, formed during 2000 and officially launched in March 2001, represents a unique collaboration of biomedical research institutes coming together with university, industry and government to develop Western Australia as an internationally recognised Bio Innovation Hub. As well as seeking to boost infrastructure funding, the Alliance aims to stimulate industry investment in research and development, promote partnering between industry, researchers and government and retain and attract quality biomedical researchers.

The Biomedical R&D Alliance is symbolic of the challenging environment in which the Institute operates. The Institute is well placed to meet those challenges – during the year we further strengthened the Board and an additional Board appointment in 2001 will provide input to the technology commercialisation activities.

One of the major initiatives currently being led by the Board is the planning for further capital fund raising. Our ability to meet many of our strategic objectives hinges on there being a substantial capital backing, the income from which can fund the achievement of these objectives. The ongoing support from Telethon as well as our many other donors is critical in this plan and we will also be looking for opportunities to attract new sources of support.

An example of a key strategic objective, which is currently being addressed, is the implementation of the remuneration scheme. This scheme will ensure an appropriate remuneration level for our senior scientists as well as security of tenure for both senior scientists and those who are identified as being the next generation of leaders in the Institute. Funding for this initiative is dependent on income from our existing capital reserves.

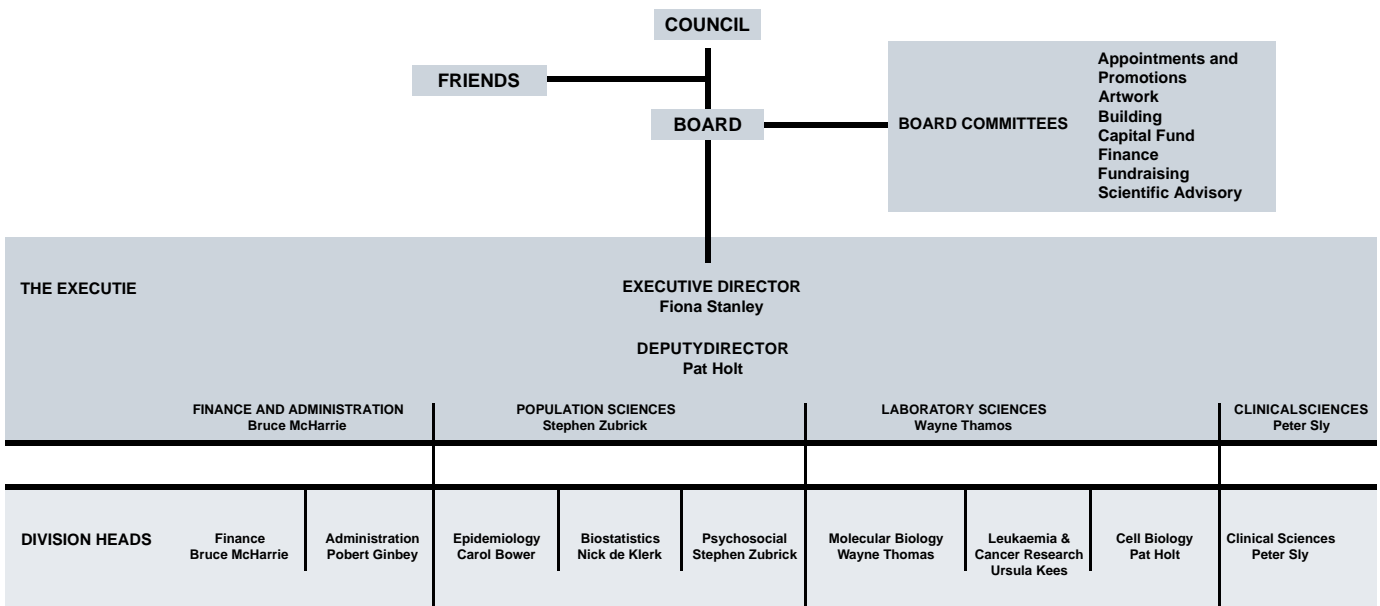
In addition to ensuring that our existing key scientists are secure and adequately rewarded, our aims include being in a position to recruit top class scientists and their teams into the Institute as part of our multi-disciplinary approach to child health research. This too is likely to entail the Institute calling upon income other than core research grants and hence the need to continue to grow our capital reserves.

Complementing many of our plans is the recent appointment of a media consultant. We anticipate that this appointment will assist the Institute to raise its profile at local, national and international levels via media exposure of various research-related activities and newsworthy events. In addition, strengthening our media links will enable us to respond to external events that in one way or another overlap the Institute's areas of interest.

In tackling these and other initiatives, I would like to acknowledge the support of my finance and administration team, my fellow executives and the Board. I look forward to seeing many of our plans come to reality in the coming years and to the resultant development of this Institute and of biomedical research as a whole in Western Australia.

Mr Bruce McHarrie

**TVW TELETHON INSTITUTE FOR CHILD HEALTH RESEARCH
MANAGEMENT/OPERATING STRUCTURE 2000**



Official Opening of New Building

John Howard



PRIME MINISTER
CANBERRA

**MESSAGE: OFFICIAL OPENING OF NEW BUILDING
TVW TELETHON INSTITUTE FOR CHILD HEALTH RESEARCH
1 September 2000**

I am very pleased to send my best wishes for the official opening of the new building for the TVW Telethon Institute for Child Health Research.

The Institute has a proud record of internationally recognised research achievement since it first opened in 1990, which reflects the high calibre of its research, their success in multi-disciplinary collaboration and the drive and enthusiasm of its leadership team. These new purpose-built facilities will enable them all to continue their valuable contribution to improving the health and wellbeing of children and families everywhere.

The many achievements of the TVW Telethon Institute for Child Health Research would not have been possible without the sustained support of the community, through the TVW Telethon Foundation and the contributions made by businesses and individuals to fundraising campaigns. I am pleased that the Commonwealth government has also played its part, through National Health and Medical Research Council research funding and the joint Commonwealth and State government capital works funding for this building. The coming together of all these interests to ensure the Institute's success exemplifies the 'social coalition' that I believe is important to effectively address social problems.

I offer my warmest congratulations to Professor Fiona Stanley and all others involved in bringing this project to fruition. I look forward to learning of future discoveries made at the TVW Telethon Institute for Child Health Research.

A handwritten signature in cursive script that reads "John Howard".

(John Howard)

IMMORTAL FIRE
by David Tunley

This short work, written for the opening of the TVW Telethon Institute for Child Health Research in Perth, incorporates fragments of music and text from two different musical cultures. The first of these is from the earliest known music

from classical Greek times, the words and music carved into a stone at Delphi.

Thought to come from about 140 BC it is a hymn to Phoebus who represented the sun, healing, prophecy and music. The other is an aboriginal children's song,

composed and sung by the late Joe Prater for a children's play ceremony. The two chants are woven into an original composition. In bringing them together

Immortal Fire symbolises in music that fire of the mind, of the heart and of compassion, which has illuminated Western medicine from earliest times and placed at the service of Australian children of all backgrounds. At the climax of

the work the children enter on a high note, like a cry for help, their song no longer carefree and playful, but broken and troubled - until taken into the warm embrace of the final cord. This piece employs the original languages. The work is

dedicated to Professor Fiona Stanley.

be-ra be-ra laulaulaulaulau be-ra be-ra be-ra laulaulaulaulau be-ra be-ra



His Excellency Sir William Deane AC, KBE



Daryl Williams QC



Dr Geoff Gallop and Mr Peter Wills AM



Mr Ben Taylor



Hon Richard Court



Professor Peter Doherty

Division of Cell Biology

Patrick Holt



Overview

The principal research theme within the Division is the aetiology and pathogenesis of immunoinflammatory diseases of the respiratory tract, with particular emphasis on atopic asthma. This work involves related research projects involving material from both experimental animal and human sources. The former studies focus upon mechanism(s) responsible for regulation of quantitative and qualitative aspects of T-cell function in respiratory tract tissues and associated regional lymph nodes. Of particular interest are populations of intraepithelial Dendritic Cells (DC) in respiratory tract tissues, which have been identified in earlier work within the Division as the principal resident antigen presenting cells in these tissues. It is clear from our studies that the DC regulate the “tonus” of local immune responses to inhaled antigen, and largely determine the nature of ensuing programming of immunological memory.

Our second major research stream focuses upon postnatal development of T-cell immunity to environmental antigens in humans, in particular airborne allergens relevant to asthma pathogenesis. We have previously described an important genetically determined deficiency in postnatal maturation of Th1 function in children at high risk for atopy. More recently we have collaborated with the Martinez group in the US in the identification of a polymorphism in the CD14 gene which is associated with intensity of atopy, and may also be involved in the Th1 maturation defect noted above. We additionally have a rapidly growing interest in paediatric vaccine immunology, and in particular in the role of developmental-associated variations in immune function as determinants of vaccine responsiveness.

Immunobiology of Dendritic Cell populations

Functional heterogeneity within respiratory tract Dendritic Cell (RTDC) subsets in the rat

DJ Strickland, F Jahnsen, JA Thomas, CL Pimm, SF Proksch, S Napoli, A Bosco, I Tobagus, PG Holt in collaboration with PA Stumbles,

Department of Medicine, The University of Western Australia

We are continuing studies on the immunobiology of RTDC populations in the rat model, focusing on cells in the airway mucosa and peripheral lung parenchyma. Our earlier studies indicate markedly different turnover times between these populations, and our current work is seeking more detailed information on function(s). Focusing initially on the airway wall populations, we have employed confocal microscopy to look in more detail at distribution, and these studies have revealed that the intraepithelial population which we have previously concentrated upon (present in densities up to 10^3 DC for mm^2 epithelium) comprises only approximately one third of the overall DC population in the airway mucosa. The surface phenotype of the intraepithelial and subepithelial DC populations appear comparable. These cells express mid-range to high MHC II expression and low level CD86 but do not express CD80. Endocytic activity is generally high, and unexpectedly is very high in the population expressing the highest levels of MHC II.

In the parenchymal lung, an additional population expressing low levels of MHC II is present, with lower numbers of highly endocytic cells present. Within and between the two populations, we have detected microheterogeneity with respect to expression of CD2, CD4, CD5 and CD8, some of which is also genetically determined, being markedly different between rat strains. We are currently sorting RTDC subsets of interest by flow cytometry, for use in *in vitro* T-cell activation assay systems.

Responses of rat RTDC populations to inflammatory stimuli

DJ Strickland, F Jahnsen, J Chi Huh, JA Thomas, CL Pimm, SF Proksch, S Napoli, A Bosco, I Tobagus,

PG Holt in collaboration with PA Stumbles, Department of Medicine, The University of Western Australia

We are seeking to determine whether the functional phenotype of RTDC subsets change during/after recruitment of waves of DC precursors into the

airway wall in response to inhalation of inflammatory stimuli. We are employing two experiment models comprising aerosol challenge of naive rats with heat-killed *Moraxella Catarrhalis*, or OVA primed rats with soluble OVA. Confocal microscopy studies suggest that the earliest response (within 1-2 hours post challenge) involves both recruitment of new precursors and emigration of resident DC to draining lymph nodes. Kinetic studies are in progress to document changes in the expression of function-associated surface molecules on the RTDC populations, particularly costimulators such as CD80/CD86, and also to examine qualitative and quantitative aspects of their antigen presentation functions.

Ontogeny of RTDC populations in the rat

J Chi Huh, DJ Strickland, S Napoli, JA Thomas, A Bosco, F Jahnsen, PG Holt

Earlier studies from our group suggest that RTDC networks are established almost exclusively postnatally, and develop relatively slowly between birth and weaning, and ongoing studies are seeking to elucidate this developmental process. Confocal microscopy studies, coupled with flow cytometric analysis of tracheal mucosal DC released by collagenase digestion, indicate major differences between these cell populations and those in adults. These include much lower levels of expression of MHC II, transient expression of CD80 (rarely encountered in the adult), and lower levels of expression of CD2. Ongoing functional studies suggest that RTDC in infant animals have blunted capacity to respond to activation signals from certain cytokines, in particular signals which upregulate CD80/86 and MHC II expression in adults, and the mechanism(s) underlying this anergic-like state are under investigation.

Inflammatory responses of DC populations in the human airway

F Jahnsen, PG Holt in collaboration with C Burke and E Moloney, Department of Respiratory Medicine, James Connolly Memorial Hospital, Dublin, and JW Upham, Department of Medicine, The University of Western Australia

As part of a collaboration with colleagues in Dublin, we are investigating the effects of bronchial challenge of atopic asthmatics with allergens. In this study, "resting" bronchial biopsies are taken from stable steroid-naive asthmatics and those on

maintenance doses of inhaled corticosteroids, and 4 hours after bronchial allergen challenge. Cryopreserved biopsy samples from these subjects are being examined in our laboratories via immunohistochemistry, employing a panel of antibodies which facilitate identification of human DC subsets. Preliminary findings suggest rapid recruitment of DC into the human airway wall following bronchial challenge, and attenuation of this response by corticosteroids, results which closely parallel our earlier findings in the rat model.

Studies on blood derived dendritic cells (DC) in the perinatal period

JW Upham (Department of Medicine, The University of Western Australia), PT Lee, BJ Holt, PG Holt

While it appears that neonates have a reduced capacity to initiate Th1 immune responses, the mechanisms responsible remain poorly defined. Published studies in animal models and in the human system have implicated antigen presenting cell (and in particular, DC) function as one of the rate-limiting factors in postnatal development of immune competence, particularly in relation to expression of Th1 function. Additionally, DC function has been hypothesised to be a factor determining the level of expression of

allergic disease *in vivo*. Accordingly, we have studied the ontogeny of the Th1-trophic cytokine IL-12, by examining circulating mononuclear cells from cord blood, 5 year old children and adults, following optimal stimulation with LPS and IFN . As shown in the table below, human cord blood cells are very poor producers of the Th1-trophic cytokine IL-12, and the capacity for IL-12 synthesis matures slowly during the preschool years.

In contrast, both adult and cord blood monocyte derived dendritic cells, cultured with GM-CSF and IL-4, synthesised comparably high levels of IL-12.

	Cord blood	5 year olds	Adults
IL-12 (pg/10 ⁶ cells)	19.9±30.7	302±339	2537±1314

These findings indicate that while the capacity to synthesise IL-12 is impaired in infancy and childhood, this deficit can be readily overcome following the provision of appropriate maturation/activation signals. Given that DC are a major source of IL-12, current studies are examining the numbers of circulating DC in neonates and adults, in order to determine whether the relative proportions of myeloid and lymphoid DC subsets vary with age.

Th1/Th2 regulation in the perinatal period - studies in experimental models

Therapeutic modulation of Th1/Th2 function during infancy - development of a rat experimental model

L Bowman, PG Holt in collaboration with B Björkstén, Karolinska Institute, Stockholm)

Ongoing studies indicate that infant rats primed during the first week of life with soluble antigen display adult-equivalent levels of T-helper 2 (Th2)-dependent immunological memory development as revealed by production of secondary IgG1 antibody responses to subsequent challenge, but in contrast to adults, the infant animals fail to prime for Th1-dependent IgG2b responses. Two lines of investigation are being pursued in this model. Firstly, cell separation studies are in progress to assess the functional capacity of T-cells and antigen presenting cells in infant animals relative to adults, to determine the contribution of these two populations to this "maturational" defect in Th1 function. Secondly, we are investigating possible therapeutic approaches towards selective boosting of Th1 function in the infants, focusing in particular on an orally

administered bacterial vaccine which is used in Europe as an immunostimulant in immunocompromised humans (including children). The oral bacterial vaccine (Broncho-Vaxom OM-85) comprises lyophilised fractions of several common respiratory tract bacterial pathogens. Results to date indicate that oral administration of OM-85 to young animals induces selective upregulation of primary and secondary IgG2b responses, accompanied by increased IFN and decreased IL-4 production (both antigen-specific and polyclonal), and increased capacity for development of Th1-dependent delayed hypersensitivity to the challenge antigen. Follow-up studies will seek to identify the cellular target(s) for the effects of the bacterial vaccine, and to elucidate the underlying mechanisms.

Neonatal Tolerance in the mouse model

I Tobagus, WR Thomas, PG Holt

The neonatal period has traditionally been viewed as a period in life during which the immune system is particularly susceptible to tolerisation. Recent literature indicates that

exposure to antigen during the neonatal period primes rather than tolerises the immune system for a pattern of T cell immunity that is skewed towards type 2 (Th2) responses. The principal aim of this project is to investigate the mechanisms regulating the development of immunological memory following primary exposure to allergen/antigen during the neonatal period using a mouse model, utilising different routes of antigen exposure.

Mucosal exposure of antigen via feeding of OVA (ovalbumin) in PBS as early as 1 day of age leads to significant OVA-specific tolerance, as revealed by subsequent challenge with OVA in adjuvant by parenteral immunisation in adulthood. The type of adjuvant was found to play an important role in skewing the subsequent immune response towards

Th1 or Th2 phenotype. The suppression was found to be adoptively transferable, suggesting a role for cytokine-producing regulatory cells as the mechanism of neonatal oral tolerance.

In contrast to the effects of mucosal antigen exposure, when neonatal mice were parenterally immunised with OVA in IFA and subsequently challenged in adulthood with OVA in CFA, strong secondary immune responses developed, indicating that successful priming had been achieved in the neonates. The memory response was dominated by IgG1 and IgG2a and the cytokine profile of spleen and lymph node cells was skewed towards the Th2 phenotype.

Studies on the aetiology and pathogenesis of allergic diseases in humans, in particular atopic asthma

Regulation of Interferon Gamma (IFN γ) gene function during the perinatal period

GP White, A Bosco, BJ Holt, PG Holt in collaboration with C Hsieh, USC, California.

IFN γ is a potent pleiotropic T-helper-1 (Th1) cytokine, the production of which is tightly regulated during fetal development. Negative control of fetal IFN γ production is generally attributed to indirect effects of Th1-antagonistic mediators produced by the placenta, but some evidence exists of more direct transcriptional regulation of the IFN γ gene in fetal T-cells, notably via hypermethylation of specific CpG sites within the IFN γ promoter. We have tested this hypothesis, employing a sensitive bisulphite genomic sequencing technique, to obtain a comprehensive picture of methylation patterns in and around the promoter region of the IFN γ gene of human adult and cord blood CD45RO⁺ T-cells. Our findings indicate that fetal T-cells exhibit hypermethylation at a range of CpG sites within and adjacent to the IFN γ promoter relative to adult T-cells, and additionally exhibit mCpApC and mCpTpC sites within the promoter; comparable sites were not methylated in IL-4, TNF α or IFN γ R1 promoter sequences from the same samples of bisulphite-treated genomic DNA. We have additionally demonstrated that over-expression of DNA Methyl Transferase 3a (Dnmt3a) but not Dnmt3b, in embryonic kidney carcinoma cells, is accompanied by a similar pattern of CpApC

methylation in the IFN γ promoter. This suggests that fine control of IFN γ gene transcription in human neonatal T-cells is associated with a unique pattern of promoter hypermethylation at sites in the context of mCpG dinucleotides, complemented by additional specific trinucleotide sites at which *de novo* methylation has not previously been demonstrated.

In ongoing studies, we are investigating the possibility that hyperactivity of this and/or related DNAmethylation mechanisms, may contribute to the lowered capacity to produce IFN γ during infancy in children at genetic risk of atopic disease.

Studies on T-cell Transcription Factors (TF) associated with Th1/Th2 regulation in the aetiology and pathogenesis of allergic disease

C Macaubas, C Wee, BJ Holt, PG Holt in collaboration with PD Sly, Division of

Clinical Sciences, TVW Telethon Institute for Child Health Research

Recent studies from a number of laboratories, principally in animal model systems, have identified a series of TF which are associated with differentiation of Th-cells towards commitment to discrete patterns of cytokine production. During 1999, we initiated studies with human T-cells which have confirmed the general applicability of the murine findings to the human system. Focusing

initially on the Th2-related TF GATA-3, we initially demonstrated by northern analysis and by sqRT-PCR, that during cytokine-driven Th2 polarisation, GATA-3 expression is upregulated and maintained, whereas during Th1 polarisation the GATA-3 gene is silenced. Progressing to CD4⁺ Th-memory responses, we have now demonstrated that these effects are also “antigen sensitive”. Thus, when T-cells from SPT⁺/IgE⁺ atopic subjects and challenged *in vitro* with specific allergen, GATA-3 gene expression is upregulated, while a reciprocal pattern (i.e. active downregulation) is seen in T-cell cultures from SPT⁻/IgE⁻ non-atopics. We have recently extended these observations employing quantitative real-time PCR employing Taqman. In our current studies, we have widened the panel of T-cell associated TFs under investigation to include (as well as GATA-3) Stat4, Stat6, T-bet, and SKAT-2, and are in the process of refining methodology for c-Maf and ROG. As well as studies upon T-cells from atopics vs non-atopics, we are investigating the possibility that variations in patterns of expression of these TFs in neonatal T-cells may underlie variations in “risk” for subsequent development of Th-2 polarised immunological memory against certain antigens/allergens.

Studies on fetal antigen-reactive T cells

CA Jones, BJ Holt, GP White, MJS Sharp, PG Holt

Numerous groups have demonstrated that umbilical cord blood mononuclear cells from term and preterm neonates respond to a variety of antigens, including allergens such as those of hen’s egg and house dust mite, and previous studies from our group have confirmed the fetal origin of the responding cells. We are currently investigating the underlying mechanisms associated with responses to allergens and extending this to include autoantigens, such as myelin basic protein (MBP). Initial studies are seeking confirmation that these fetal antigen-specific responses involve classical interactions between antigen presenting cells and T cells as occurs with adults, and assessing the contribution of “memory” T cells to these responses, given that this latter subset is much reduced in the neonate compared to the adult. Preliminary results indicate that antigen-specific reactivity is dependent on MHC Class II presentation to CD4⁺ T cells and does not reside within the CD45RO⁺ T cell subset. An additional area of focus is the role of a subset of CD4⁺ T cells termed T regulatory cells that produce the immunoregulatory cytokines IL-4, IL-10 and TGFbeta. Of particular interest, we have observed

that programmed cell death (apoptosis) after antigen stimulation is more predominant amongst cord blood T cells compared to adult peripheral blood T cells. Preliminary findings suggest that this is initiated by CD4⁺ T cells and mediated by the Fas/Fas ligand pathway. We are now confirming this finding and seeking further information on underlying mechanisms, and evaluating how long these “apoptosis-sensitive” responses persist postnatally. Further studies will address differences in these responses in cord blood of children at risk of, or who subsequently develop, atopic disease.

The role of infections in the aetiology of atopy

MJS Sharp, J Rowe, D Suriyaarachchi, PG Holt in

collaboration with PD Sly and M Kusel, Division of Clinical Sciences, TVW Telethon Institute for Child Health Research and S Johnstone, Imperial College Medical School, London

We have been cryobanking PBMC samples collected during infancy from a birth cohort of children who are being intensively monitored for infectious disease and markers of atopy/wheeze. Postnasal aspirate samples are currently undergoing PCR analysis to identify infectious agents associated with symptomatology during the first year of life. We have commenced studies on adaptive and innate immune functions on cord blood mononuclear samples from the cohort, addressing the hypothesis that the functional capacity of the immune system at birth may be an important determinant of subsequent susceptibility to both infections and allergic sensitisation, during infancy.

Responses to microbial superantigens in allergic disease

T Heaton, TJ Venaille, PG Holt in

collaboration with D Mallon, Clinical Immunology, Princess Margaret Hospital and Fremantle Hospital

There is now a large body of evidence to suggest that bacterial superantigens may be involved in the exacerbation and/or initiation of some atopic diseases. We are investigating the cellular responses of allergic individuals to bacterial superantigens in an attempt to elucidate the role of these superantigens in the pathogenesis of atopy.

Our research has been focussed primarily on the role of Staphylococcal Enterotoxin B (SEB) in Atopic

Dermatitis (AD), although recent evidence which demonstrates that this toxin may also be involved in asthma. We have shown that *in vitro* cytokine production by peripheral blood mononuclear cells (PBMC) of adult patients with active AD responds differently to SEB than corresponding production by PBMC from non-atopic individuals and mild atopics without AD. This difference is marked by a large increase in secretion of the Th2-type cytokine IL-5. Subsequent studies using PBMC from patients with active asthma revealed the same pattern of IL-5 responses. We speculated that this difference may be due to an increase in the activation state of the T cells from patients with active disease; however, further experiments testing the effects of SEB on PHA blasts suggested that this was not the case, hinting at more complex underlying mechanisms(s). “Resting” the cells from adult AD patient samples prior to stimulation with SEB also did not abrogate the IL-5 response. These data imply that there is a phenotypic difference in the IL-5 producing cell populations in the different groups of subjects, which is independent of their activation state. Work is currently underway to investigate whether these responses can be correlated with skin colonisation by bacterial strains which produce superantigens.

Vaccine immunity in early childhood

J Rowe,
TM Monger,
D Suriyaarachchi,

PG Holt in collaboration with PD Sly, Division of Clinical Sciences, TVW Telethon Institute for Child Health Research and R Loh, Clinical Immunology, Princess Margaret Hospital)

Previous studies from our laboratory on inhalant allergen-specific Th cell function during early life have demonstrated that responses in neonates follow the typical fetal pattern, being dominated by Th2 cytokines, together with a very low and variable Th1 component. The aim of this ongoing work is to follow the development of vaccine immunity in early postnatal life, and determine whether children genetically at high risk of developing atopy responded differently to vaccination compared to those at low risk. We have examined the responses to the Tetanus component of the Diphtheria, Tetanus, acellular Pertussis vaccine in a prospective cohort of 130 healthy infants. These studies have demonstrated that the Th2 component of the vaccine response (IL-4, IL-5, IL-9 and IL-13) developed rapidly and remained stable throughout the study period. Furthermore, the contribution of the Th2

component of vaccine-specific and polyclonal cytokine responses was more prominent in children with an atopic family history. In contrast, the Th1 component of the vaccine response (IFN γ) was commonly transient, declining after the final primary vaccine dose at 6 months. However, between 12 and 18 months, the Th1 component of the vaccine specific response, as measured by IFN γ , demonstrated a marked resurgence in many subjects, which was restricted to those displaying a developmentally-related increase in overall polyclonal IFN γ production capacity during this period. We are currently undertaking additional studies which focus on the possible mechanisms involved in the expanded IFN γ responses between 12 and 18 months. An unexpected additional finding from this work was an apparent inverse relationship between postnatal maturation of IFN γ production capacity during infancy, and development of T cell memory against RSV F/G protein, a surrogate marker for RSV infection. This suggests that the maturational deficiency in IFN γ function which we have previously identified as an aetiological factor in atopy development, may also be a risk factor for respiratory viral infection (and hence bronchiolitis) during infancy.

Scientific Highlights

- the IFN γ promoter in neonatal CD4⁺ CD45RA⁺ T-cells is hypermethylated relative to that in adult naive CD4⁺ Th-cells, and the neonatal cells exhibit methylation at both CpG and non-CpG sites;
- reciprocal patterns of Transcription Factor expression distinguish Th1 and Th2 cells both during initial polarisation and during subsequent recall responses;
- bronchial challenge of human atopics with inhalant allergen recruits high numbers of myeloid DC into the airway mucosa;
- the postnatal development of persistent vaccine-specific Th1 memory during infancy is limited via mechanism(s) associated with maturation of systemic (polyclonal) Th1 function, in particular capacity to produce IFN γ .

Theses Passed

M Jenmalm. Development of IgG subclass antibodies to allergens during early childhood, PhD, University of Linköping.

Invited Presentations

PG Holt. Symposium Speaker: Antigen presentation in the lung - Transatlantic Conference on Antigen Processing and Presentation, Lucerne, 2000.

PG Holt. Plenary Speaker: Asthma in the 3rd millennium. New directions resulting from improved understanding of its immunopathology - Respiratory Drug Delivery Congress VII, Tampa, 2000.

PG Holt. Symposium Speaker/Chair: Regulation of cytokine production in T-cell responses to inhalant allergen - Collegium International Allergologicum, Hakone, 2000.

PG Holt. Plenary Speaker: Allergy and microbes in the development of asthma - Italian Society for Pediatric Respiratory Disease Congress, Siena, 2000.

PG Holt. Plenary Speaker: Sensitisation and tolerance through the lung. Regulation of Th-cell responses to inhaled allergen by airway intraepithelial Dendritic Cells - European Academy of Allergology and Clinical Immunology, Lisbon, 2000.

PG Holt. Symposium Speaker: Role of microbial stimulation in the aetiology of allergy - European Academy of Allergology and Clinical Immunology, Lisbon, 2000.

PG Holt. Symposium Speaker: The Dendritic Cell carpet - 17th Congress of Allergy & Clinical Immunology, Sydney, 2000.

PG Holt. Symposium Speaker: Programming of allergen specific Th-memory during childhood - 17th Congress of Allergy & Clinical Immunology, Sydney, 2000.

PG Holt. Chair/Rapporteur: The dirty decade - 17th Congress of Allergy & Clinical Immunology, Sydney, 2000.

PG Holt. Plenary Speaker: Significance of allergen exposure in early childhood to expression of atopy in later life - International Symposium on Susceptibility Factors for Respiratory Disease, Lovelace Respiratory Research Institute, Santa Fe, 2000.

PG Holt. Symposium Speaker: Dendritic Cells as sentinel cells in asthma - Air Board International Workshop, Hayman Island, 2000.

PG Holt. Plenary Speaker: The aetiology of allergic respiratory disease - Colorado Allergy Society Conference, Aspen, 2000.

External Committees

PG Holt. Scientific Advisory Board, Jenner Institute for Vaccine Research, U.K.

PG Holt. Councillor, International Society for Mucosal Immunology.

PG Holt. International Scientific Board, Pharmacia Allergy Research Foundation.

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Division of Children's Leukaemia and Cancer Research

Ursula Kees



Overview

The development of successful therapies for children with cancer has been accomplished over the past forty years, with a reversal of the outcome from 80% mortality in the past to an estimated 80% survival today. These results can be attributed to large international co-operative studies. The Oncology Total Care Unit at the Princess Margaret Hospital (PMH) and our research laboratory maintain a close relationship and we are members of the largest study group into childhood cancers, the US-based Children's Oncology Group (COG). Leukaemia is the most common form of cancer in children. More than 95% of children newly diagnosed with acute lymphoblastic leukaemia (ALL) will today achieve a complete remission and about 70% will be cured, however about 30% will relapse. The challenge is to find treatments for patients not currently being cured with the aim for reduction in therapy since it is associated with toxicities and complications. The development of more effective and less toxic anti-cancer drugs depends on a better understanding of the genetic differences between normal and cancer cells. This in turn will change our approach to the diagnosis, classification and treatment of childhood cancer. The research program of the division comprises four areas. First, gene expression profiles in childhood ALL, with particular focus on the *HOX11* oncogene. The gene was discovered at a chromosomal breakpoint in one of our cell lines from a patient diagnosed with ALL of T-cell type (T-ALL). *HOX11* is a DNA-binding oncoprotein aberrantly expressed in a significant proportion of T-ALL patients. Our recent studies confirm that *HOX11* deregulation occurs in the absence of any translocation, hence other mechanisms must cause gene activation and these are currently under investigation. In order to address these questions we have developed a cellular model to study the role of *HOX11* in tumour development. Secondly, in previous work we showed that deletion of the tumour suppressor gene *p16* is associated with unfavourable outcome in paediatric ALL. Our most recent studies were conducted using real-time polymerase chain reaction (PCR) which confirmed and extended these findings. This method is a precise high-throughput assay with applications in a wide range of cancers. Thirdly, a new research program focuses on paediatric brain tumours. The major aim is to identify tumour suppressor genes by using representational difference analysis. Fourthly, our research is targeted at the development of new approaches to find anti-cancer drugs. The current project aims at developing a platform technology for isolating specific peptide inhibitors of oncoprotein interactions. The study provides the groundwork for a high-throughput screening system for novel peptide-based drugs.

Key words: childhood cancer, leukaemia, brain tumours, oncogenes, tumour suppressor genes, anti-cancer drug screening.

*Gene expression in paediatric ALL

The *HOX11* oncogene is expressed in half the cases of paediatric T-ALL and occurs in the absence of cytogenetically detectable aberration

UR Kees, R Kumar and PM Watt in collaboration with DL Baker, Princess Margaret

Hospital and NA Heerema, F Uckun, M La and H Sather, Children's Oncology Group, Arcadia, USA.

Recurrent involvement of tumour-specific chromosomal translocations has led to the identification of oncogenes critical in tumorigenesis. In paediatric T-ALL such translocations are present in 30-35% of cases, while 30-45% show a normal karyotype and the remaining patients show other cytogenetic abnormalities. In 4-7% of T-ALL patients *HOX11* is aberrantly activated by either of two chromosomal translocations, t(7;10) and t(10;14), which place the *HOX11* coding sequence under the transcriptional control of T-cell receptor regulatory elements. We show that aberrant *HOX11* expression was present in 49% of the T-ALL specimens, yet was not found in ALL of B-cell lineage. Direct cytogenetic analysis of the T-ALL specimens showing *HOX11* expression revealed that only two of 17 exhibited abnormalities of the *HOX11* locus at 10q24. These results confirm and extend our previously published findings and implicate mechanisms other than chromosomal translocations for the deregulation of *HOX11*. The accurate measurement of *HOX11* by real-time PCR revealed that expression levels in T-ALL specimens ranged over four orders of magnitude, whereas purified T-cells from 11 normal donors were clearly negative. Analysis of clinical outcome for the whole study group did not show significant differences for *HOX11*-positive versus *HOX11*-negative patients, although, depending on the therapy used, *HOX11* upregulation appears to be associated with better survival.

Expression analysis reveals genes aberrantly expressed in paediatric ALL

WK Greene, D D'Souza, J Ford and UR Kees in

collaboration with A Boodhoo, Murdoch University.

In a significant proportion of T-ALL cases, it is known that developmentally important genes such as *HOX11*, *SCL* and *LMO2* are translocated into either of two T-cell receptor loci located on human chromosomes 7 and 14. These highly conserved

genes encode nuclear transcription factors that are involved in the regulation of gene transcription. This implicates aberrant activity of transcriptional complexes at cis gene regulatory sequences in the pathogenesis of this tumour type. However, our understanding of the molecular basis of malignancy in T-ALL is largely still incomplete. In particular, it remains unclear as to exactly what set of oncogenically relevant downstream target genes and transcriptional coregulators are required for cell transformation to occur. We have therefore performed semi-quantitative gene expression analyses by RT-PCR in a panel of cell lines and primary specimens from patients with T-ALL and B-lineage ALL. In addition to 4 normal thymus and bone marrow samples. Genes analysed in this study included major oncogenic transcription factors specifically associated with T-ALL (*HOX11*, *SCL*, *LMO2*), known target genes of these factors (*ALDH1*, *RALDH2*, *WT1*, *c-kit*), retinoid pathway genes (*RAR alpha*, *beta*, *gamma*) and potential *HOX11* co-factor genes (*PBX 1, 2, 3*; *MEIS 1, 2, 3*). A number of notable correlations were found by this work, some of which extend previous findings e.g. co-expression of *RALDH2* and *SCL*, while others further implicate aberrant retinoid signalling in the pathogenesis of this tumour type.

*Transcriptional control of *HOX11* and *PBX3*

HOX11* as a target gene of the homeodomain protein *PBX2

RL Brake, UR Kees and PM Watt

Ectopic expression of the homeobox gene *HOX11* is associated with a significant proportion of childhood T-ALLs. We hypothesize that one mechanism of gene deregulation involves overcoming the normal silencing mechanism(s) of gene expression. Here we describe a search for the trans-acting factors which mediate transcriptional activity of a distal portion of the *HOX11* promoter. We have identified a region of this promoter specifically regulated by *PBX2*, a member of the *PBX* family of TALE homeodomain proteins. This *PBX* Regulatory Element (*PRE-1048*) in the *HOX11* promoter contains a novel DNA binding sequence. *PRE-1048* mediates differential regulation of the *HOX11* gene in leukaemic cell lines. This is the first report of a homeobox gene specifically regulated by *PBX2* which joins an emerging class of vertebrate homeobox target genes regulated by *PBX* proteins. The *PRE-1048* binding complex also contains the *PBX* regulatory protein *PREP1*. A 16 base-pair element to which the *PBX2*/*PREP1*-containing

complex binds accounts for half of the entire transcriptional activity of the *HOX11* promoter. Additional tissue-specific cofactors appear to be required for the regulation of *HOX11* via this element since transcriptional activation occurred in a *HOX11*-expressing cell line, K562 but was absent in a *HOX11*-negative cell line, PER-117.

Characterising novel alternative transcripts of the *HOX11* oncoprotein in leukaemia

K Hoffman,
UR Kees,
W Greene and
PM Watt

The production of transcription factor isoforms by regulated alternative splicing of pre-mRNAs is now recognized as a widespread phenomenon, although the biological consequences in tumorigenesis are understood in only a few cases. Alternative splicing of mRNAs has enormous potential for structurally altering transcription factors by generating structurally diverse protein variants from one genetic locus. Transcripts that either contain or lack functionally important exons of a gene may thus encode proteins with very different functions. Recent evidence from our laboratory demonstrates that three previously unidentified transcripts of different sizes are generated from *HOX11* in leukaemia cells. In addition to the well-known 2.3 kb transcript present in leukaemia cells that show translocations involving band 10q24, we have observed other transcripts which contain sequences previously thought to be intronic. We have also obtained evidence of a novel transcript of *HOX11* which is expressed in fibroblasts and in normal T-cells. Using Rapid Amplification of cDNA Ends (RACE) and RT-PCR, we have cloned and determined the sequence of these novel transcripts. Altogether we have now sequenced 47 individual clones, providing a comprehensive view of the alternative transcript structures. Northern blotting showed that these transcripts are produced in substantial quantities relative to the 2.3kb transcript. Importantly, these novel transcripts are expressed in primary specimens from patients with T-ALL. Given the paucity of evidence for tumorigenicity of the 2.3kb *HOX11* transcript in T-cells, we suggest that there are additional, as yet unrecognised factors contributing to the development of T-cell malignancy. We postulate that other forms of *HOX11* which are also deregulated by a mutational event such as a 10q24 translocation, could be required for full transformation of T-cells. We propose to test this hypothesis using *ex vivo* and transgenic assays.

Characterisation of transcription factor complexes in leukaemia cells

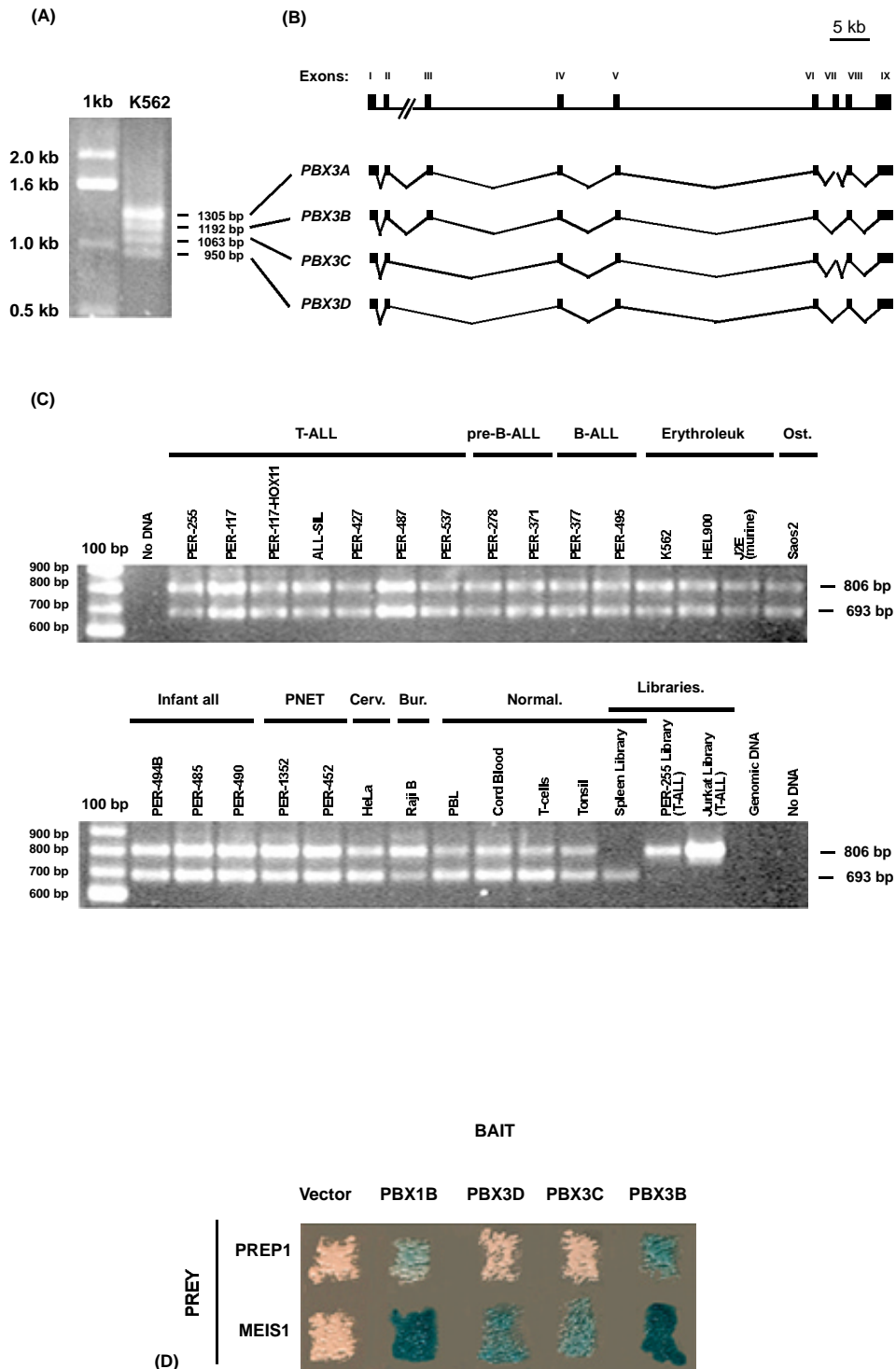
NM Milech,
PM Watt and UR
Kees

HOX11, like other transcription factors requires protein/protein interactions to allow specific control of expression of its target genes. Deregulated expression of a *HOX11* partner may be required in concert with *HOX11* deregulation in order to form a transcription factor complex which is oncogenic. Several proteins have been reported to be associated with *HOX11*, although none has been independently confirmed. We have been using yeast two hybrid screening and *in vitro* (coimmunoprecipitation) assays to confirm these interactions and to search for novel proteins involving *HOX11*. One such novel partner of *HOX11* has already been identified and is being characterised. It is a transcription factor which has already been implicated in cancer.

The identification of novel alternative *PBX3* isoforms with distinct interactions specificities

NM Milech,
UR Kees and
PM Watt

PBX3 is a member of the *PBX* family of TALE homeobox genes. The prototypic member, *PBX1*, was first identified in chromosomal translocations in B-lineage leukaemia and is required for normal haematopoiesis. *PBX2* and *PBX3* were later identified as members of this highly conserved family by their strong homology to *PBX1*. While the expression pattern of *PBX1* is restricted, *PBX2* and *PBX3* are ubiquitously expressed. Little is known about the functional role of *PBX3*. Our studies identified two *PBX3* transcripts alternative to the canonical forms, *PBX3A* and *PBX3B*, resulting from a novel splice in *PBX3* (see figures A and B page 24). These new isoforms, named *PBX3C* and *PBX3D*, have been detected in all tissues and cell lines tested (see figure C page 24). Intriguingly, expression of *PBX3D* is favoured in normal cells, while *PBX3C* expression is favoured in leukaemia cells. Functional studies showed that *PBX3C* and *PBX3D* proteins were unable to interact with the *PBX* co-factor PREP1 and weakly interacted with MEIS proteins (see figure D page 24). We propose that *PBX3C* and *PBX3D* may affect *PBX*-mediated transcriptional regulation by acting in opposition to the known *PBX* proteins, and may favour alternative complex formation. The identification and characterisation of these novel *PBX3* isoforms provides a foundation for a better understanding of the biological role of *PBX3*.



Figure

- A. An RT-PCR amplification of alternative PBX3 transcripts.
- B. A map showing the relationship of alternative transcript sequences to the genomic sequence. Exons are shown as black boxes joined by lines indicating splice donor/acceptor junctions.
- C. Expression profiles of the alternative PBX3 transcripts.
- D. Interaction specificities of the alternative transcripts shown using two hybrid screening assay in yeast. Dark patches indicate strong interaction white patches indicate no interaction.

*Cellular models to dissect the role of HOX11 in tumour development

Ectopic expression of HOX11 inhibits erythroid maturation and enhances adhesion in J2E cells

WK Greene,
J Ford,
D D'Souza,
PM Watt and
UR Kees in

collaboration with DN Dixon, Murdoch University.

In childhood T-ALL, aberrant expression of the homeodomain protein HOX11 is a frequent event. However, the mechanism by which HOX11 exerts its leukaemogenic effect remains unclear. Previous studies have indicated that HOX11 may cause leukaemogenesis by altering haematopoiesis and/or apoptosis. In this project we sought to further investigate the role of HOX11 in the initiation of leukemogenesis. Our recent work has focussed on the effect of enforced *HOX11* expression on PER-117 T-cells and the J2E erythroid cell line. In both these cell lines we have shown that HOX11 upregulates *ALDH1* target gene transcription, with the effect being much greater in J2E cells. Data from our PER-117 studies suggest that ectopic expression of HOX11 does not affect cellular adhesion, the cell cycle nor susceptibility to apoptosis under various conditions including serum starvation, gamma irradiation, vincristine, daunorubicin, and anti-CD95. Because the immortalizing ability of HOX11 is not restricted to T-cells, we have also examined its effect in the erythroid lineage using the J2E cell line, which notably is capable of terminal differentiation. In contrast to PER-117 T-cells, J2E cells were profoundly altered by HOX11 in terms of cellular morphology and differentiation status. Taken together, our morphological, biochemical, immunocytochemical and cellular adhesion analyses show that HOX11 de-differentiates J2E cells toward a multipotent progenitor stage. This result lends support to the notion that HOX11 functions to immortalise cells by disrupting haematopoietic differentiation. This is likely to be due to HOX11 directly or indirectly changing the expression of regulatory and structural genes associated with cell lineage commitment. Thus we have employed representational difference analysis and cDNA array technology to find genes whose expression is altered by HOX11. A number of candidates have been identified, which intriguingly, encode proteins involved in the regulation of the cell cycle, or play a role in cell differentiation or cell adhesion. These genes are presently undergoing further validation and characterisation. Future studies will seek to identify those targets that are oncogenically relevant

in a order to elucidate the mechanism by which this homeoprotein immortalises cells.

*Tumour suppressor genes in paediatric leukaemia

Hemizygous *p16^{INK4A}* deletion in paediatric acute lymphoblastic leukaemia predicts independent risk of relapse

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with DL Baker,

Princess Margaret Hospital, PR Burton, University of Leicester, GH Reaman and H Sather, Children's Oncology Group, Arcadia, USA

The assessment of deletion of dominant genes requires the detection of hemizygosity in primary patient specimens contaminated with normal cells. Meeting this challenge in high-throughput cancer screening is becoming increasingly critical with the recent identification of several tumour suppressor genes which are haploinsufficient. The genes at the *INK4A/ARF* locus at 9p21 are frequently involved in human cancer. Virtually all *p16^{INK4A}* exon 2 (henceforth called *p16*) inactivation in paediatric ALL occurs by gene deletion. The results of this study illustrate that real-time quantitative polymerase chain reaction (PCR) is capable of detecting gene deletion in primary patient specimens with a precision not previously achieved by conventional methods. Importantly, this assay includes the detection of hemizygous deletions. Strikingly, the study revealed that the risk ratio for relapse for hemizygous deletion compared with no deletion was 6.558 ($p=0.00687$) and for homozygous deletion 11.558 ($p=0.000539$). Furthermore, quantitative RT-PCR assays demonstrated that in hemizygous specimens the remaining allele was expressed. The *p16* gene therefore joins a growing class of haploinsufficient tumour suppressor genes, which includes *TGF β 1* and *p27/KIP1*. This finding emphasises the importance of reinterpreting previous studies in a range of cancers where the rate of hemizygous loss of *p16* was not addressed. These results also confirm and extend our previous findings that homozygous deletion of *p16* in paediatric ALL patients is an independent prognostic indicator of outcome from therapy.

INK4a/ARF deletions are acquired at relapse in childhood ALL: a paired study on 25 patients

TL Carter and UR Kees in collaboration with GH Reaman,

Children's National Medical Centre, Washington, DC, USA.

Current risk adjusted intensive therapies for childhood ALL are expected to result in an event free survival of greater than 75%. In sharp contrast, relapsed paediatric ALL is a difficult disease to treat. In this study, twenty-five paediatric patients with ALL were analysed at diagnosis and relapse for their *p16* (exon 2) status using the most accurate method of detection, real-time PCR. The median time to relapse for the group was 27 months. At diagnosis the incidence of *p16* homozygous and hemizygous deletion in this group was 32% and 20%, respectively. The incidence of homozygous *p16* deletion at relapse was 64%. A large number of patients, eight of 16 (50%), developed *p16* homozygous deletion at relapse. Of those 8 patients 4 were hemizygous for the deletion and 4 were germline at diagnosis. At diagnosis those patients with a homozygous or hemizygous *p16* deletion relapsed sooner than those germline for *p16*. We have shown that *p16* alterations are frequently present in relapsed lymphoblastic leukaemia in children.

***Paediatric brain cancers**

The identification of tumour suppressor genes involved in the growth & development of primitive neuroectodermal tumours

PB Dallas and UR Kees.

The molecular genetic mechanisms

underlying the initiation and growth of primitive neuroectodermal tumours (PNETs), the most common type of childhood brain tumour, are poorly understood. A few tumour suppressor genes, including *PTEN/MMAC1*, *DMBT1*, and *PTCH* are mutated in a small percentage of PNETs. However, it is clear from the molecular and cytogenetic data that other tumour suppressor genes are involved in PNET pathogenesis. We are searching for these genes using representational difference analysis (RDA).

We have generated 59 DNA clones by applying a RDA procedure designed to detect DNA sequences that are deleted in our three PNET cell lines. The DNA sequences of these clones have been determined, and we have taken advantage of the recently completed draft version of the human

genome to identify the chromosomal origins of our clones. So far, we have identified 7 hemizygotously deleted regions pointing to 6 chromosomal locations of interest (10q, 16q, 14q, 7p, 3q, and 1p). Some of these regions (in particular 10q and 16q) have been implicated in PNET pathogenesis in previous studies. These findings are encouraging, and we are currently mining the human genome databases for candidate tumour suppressor genes mapping to these high priority chromosomal regions. We have access to PNET specimens in local and international tumour banks that will allow us to assess the frequency of deletion of targeted sequences in a large number of PNET specimens.

We are hoping to complete our RDA studies by the end of 2001 by which time we will have generated a large panel of RDA clones for further analysis. To our knowledge this will be the first time that RDA has been systematically applied to the detection of deletions in PNET cell lines.

We anticipate that our RDA data, when combined with data obtained from expression microarray experiments proposed for the near future, will significantly improve our understanding of the molecular pathways involved in PNET growth and development, ultimately leading to improved therapeutic strategies for affected children.

***Leukaemia drug discovery program**

Development of a new cancer drug discovery platform using yeast reverse two hybrid screening

PM Watt, T Johansson and RM Hopkins in collaboration with E Golemis, Fox Chase Cancer

Centre, Philadelphia USA.

This project focusses on the establishment of a genetic system for isolating specific peptide inhibitors of oncoprotein interactions. Our model system makes use of oncoprotein interactions in order to screen peptide libraries for their capacity to block such interactions. This model has potential application for future drug screening aimed at designing better therapies for cancer as well as other diseases. Using homologous recombination we constructed a panel of eight different dual-reporter yeast strains which are conditionally resistant to the drugs cycloheximide and 5-FOA. This strain contains the counter-selectable reporter genes *URA3* and *CYH2* which are activated by the interaction of interest, causing the yeast to die in the presence of

drug. We have constructed a bait-expressing constructs using a low copy-number inducible expression vector. This vector possesses the advantage of enabling adjustment of expression level by titration of the amount of galactose present in the yeast media. This inducible system was devised to overcome background 5-FOA toxicity problems which can arise due to autoactivation of bait constructs. In this system, we constructed two sets of expression plasmids encoding the interacting oncoprotein pairs: FOS/JUN, LMO2/SCL and E47/SCL. We have also shown that the galactose titration approach is sufficient to overcome the auto-activation problem and also enables powerful control of stringency. The interacting oncoprotein pairs were shown to activate transcription of the counterselectable reporter genes in our selection system and to cause the death of the host yeast strain under the restrictive selection condition. A pilot screen of clones expressing random peptides from the pBlock-1 library has yielded a number of blockers of E47/SCL and FOS/JUN interactions and shown that the stringency of selection can indeed be adjusted. Recently, we have constructed another two vectors for high through-put screening which are suitable for mammalian and yeast expression and contain an alternative selectable marker conferring resistance to blasticidin. Clones isolated from libraries constructed in these vectors can be shuttled directly into leukaemia cell growth inhibition assays. In this project we have established a practical, high-throughput screening system which will provide a useful platform technology for the identification of novel peptide-based anticancer drugs. In addition, the identification of specific blockers of protein/protein interactions also provides a useful source of dominant negative probes for dissecting mammalian gene pathways and validating candidate drug targets. These studies represent the establishment of a practical, high-throughput screening system for drug leads which has elicited interest from leading biotechnology companies in the US and Europe.

Acknowledgments

The block grant funding received from the Children's Leukaemia and Cancer Research Foundation (Inc) is gratefully acknowledged, as is their generous support for filing of patents associated with the Drug Discovery Program. Our sincere thanks go to the dedicated volunteers and the Management Committee of the Foundation. The support of the Three Boys Legacy is also gratefully acknowledged.

Invited Presentations

TL Carter. Deletions of *p16INK4A* in primary specimens from paediatric patients with acute lymphoblastic leukaemia predict risk of relapse. Invited speaker at the Children's Oncology Group Meeting, Tampa, US.

PB Dallas. p270 is related to p300/CBP and is a component of a human SWI/SNF chromatin remodelling complex. Microbiology seminar program, Department of Microbiology, University of Western Australia.

WK Greene. A potential role for HOX11 in childhood leukaemia. Invited speaker at the Western Australian Institute for Medical Research, Perth.

WK Greene. A potential role for HOX11 in childhood leukaemia. Invited speaker at the Centre for Molecular Immunology and Instrumentation, University of Western Australia, Perth.

WK Greene. Microarrays and laser microdissection in leukaemia. Invited speaker at the Lotteries Commission Medical Research Symposium, Perth.

UR Kees. A precise high-throughput assay of hemizygous *p16INK4A* deletion in primary leukaemia specimens predicts independent risk of relapse. Speaker at the NCI-EORTC Conference, Nyborg, Denmark.

UR Kees. Hemizygous *p16INK4A* deletion in primary specimens from paediatric patients with acute lymphoblastic leukaemia predicts independent risk of relapse. Speaker at the Lorne Cancer Conference, Lorne, Victoria.

UR Kees. Molecular pathology of childhood leukaemia. Invited speaker at the WA State Cancer Conference, Perth.

PM Watt. Using Microarrays for the validation and screening of libraries in drug discovery programs. Invited speaker at the Lotteries Commission Medical Research Symposium, Perth.

PM Watt. Strategies for isolating specific blockers of protein/protein interactions. Invited speaker at the Western Australian Institute for Medical Research, Perth.

External Committees

UR Kees. Chairman of Study COG-B946, Children's Oncology Group, USA.

UR Kees. Chairman of Study COG-B969, Children's Oncology Group, USA.

PM Watt. Committee Member of the Combined Biological Sciences Association of Western Australia

WK Greene. Committee Member of the Australian Society for Medical Research (WA branch) and Health Expo convenor, 2000.

Patents arising from this work

PM Watt and UR Kees (1998). Inventors on patent entitled "Peptide detection method" filed internationally under the PCT (PCT/AU99/00018) and in the USA (09/227,652) as a full patent application. Priority date January 9, 1998 claimed from US provisional application number 60/070989. Proceeded to National Phase Examination in Europe, USA, Japan, Australia, New Zealand and UK.

Applicant: TVW Telethon Institute for Child Health Research

UR Kees and PM Watt (1999). Inventors on patent entitled: "Method of detecting the presence or absence of specific genes" filed internationally under the PCT. Priority date November 3, 1999 claimed from US provisional application number 60/163252.

Applicant: TVW Telethon Institute for Child Health Research

PM Watt and WR Thomas (1999). Inventor on patent entitled: "Isolating biological inhibitors from natural domain libraries filed under the PCT (PCT/AU00/00414) and as a full application in the US on May 5, 1999 (60/132711).

Applicant: TVW Telethon Institute for Child Health Research

PM Watt (2000). Inventor on provisional patent application entitled: "Improved high throughput reverse two hybrid/reverse three hybrid screening method" filed provisionally in Australia (PQ6830).

Applicant: TVW Telethon Institute for Child Health Research.

PM Watt and R Hopkins (2000). Inventor on provisional patent application entitled: "Dual fluorescent reporter construct for two hybrid and

reverse two hybrid screening applications" filed as an Australian provisional application (PR1256) on 6/11/00.

Applicant: TVW Telethon Institute for Child Health Research.

PM Watt, R Hopkins, I Serebriiskii and E Golemis (2001). Inventor, on patent application filed under PCT entitled: "Improved high throughput reverse N-hybrid screening method.

Applicant: TVW Telethon Institute for Child Health Research.

Staff and Students

Head of Division

Ursula Kees, *PhD, Adj. Associate Professor UWA*

Research Staff

Peter B Dallas, *PhD, Senior Research Officer*

Jette Ford, *BAppl Sc, GradDipComp, Research Assistant*

Catherine Fussell *BSc (Hons), Research Assistant (from October 2000)*

Wayne K Greene, *PhD, Senior Research Officer (at Murdoch University)*

Katrin Hoffmann, *PhD, Research Assistant*

Richard Hopkins, *PhD, Senior Research Officer*

Timothy Johanssen *BSc (Hons), Research Assistant*

Rolee Kumar, *BSc (Hons), Research Assistant*

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Stewart Cattach, *Laboratory Assistant*

Students

Rachael Brake, *BSc (Hons), PhD candidate*

Tina L Carter, *MBBS, FRACP, PhD candidate*

Nadia Milech, *BSc (Hons), PhD candidate*

Anna Pryde, *BSc (Hons)*

Thesis passed

AK Pryde. Genetic abnormalities in paediatric brain tumours. Honours thesis. University of Western Australia.

Division of Clinical Sciences

Peter Sly



Overview

The Division of Clinical Sciences aims to conduct high quality, clinically oriented research that focuses on paediatric respiratory diseases, especially asthma, cystic fibrosis and vaccine preventable disease. The Division consists of six subgroups loosely based around different methodologies. There is close interaction and some overlap of staff between the groups.

The **Infant Lung Function Group** works on the development and application of new techniques for measuring lung function in infants up to the age of two years. These new techniques are used to measure the growth and development of airways and lung tissues, determine the site of action within the lungs of asthma drugs and determine whether lung function abnormalities predict which infants will have persistent asthma.

The **Lung Growth and Development Group** studies the normal growth and development of the lung and how the lung responds to adverse influences. This group uses morphometric techniques to determine lung structure in animal models. They also use measurements of lung function to determine structure-function correlates.

The **Cystic Fibrosis Group** studies the mechanisms underlying the host inflammatory response in cystic fibrosis as well as issues related to diet, growth and nutritional requirements. The group also develops strategies to prevent progressive lung damage in this condition. Laboratory-based techniques, animal models and clinical methodologies are used to conduct multi-disciplinary research in close collaboration with the Cystic Fibrosis Clinic at Princess Margaret Hospital for Children.

The **Pulmonary Pharmacology Group** uses sophisticated measurements of lung function in small animals to investigate the mechanisms of atopic sensitisation, bronchial hyperresponsiveness and asthma. The group also uses classic pharmacological techniques to make *in vitro* observations to extend the *in vivo* findings.

The **Clinical Asthma Research Group** conducts projects involving infants and children with asthma. Projects focus on the mechanisms underlying the development of asthma and on better methods for managing, monitoring and treating asthma. This group runs a number of cohort studies looking at the antenatal antecedents of asthma, the influence of infections on the development of allergic sensitisation and the genetic basis of asthma.

The **Vaccine Trials Group** is a collaborative venture between the Division of Clinical Sciences, Princess Margaret Hospital for Children and the Department of Paediatrics, University of Western Australia. The group performs Phase 1, 2 and 3 trials with new vaccines, conducts trials into non-vaccine treatments of vaccine-preventable diseases and

conducts research into the development of immunity to vaccines and vaccine-preventable diseases.

Infant Lung Function

Comparison of different techniques to measure exhaled nitric oxide in infants (eNO)

(S Stick, P Franklin, S Turner, R Mutch).

Work has continued comparing tidal breathing techniques with a single breath technique developed by our group. Data suggests that when infants are sedated during quiet, regular breathing the tidal breathing technique has similar variability and ability to discriminate between symptom groups as the single breath technique. However, the tidal breathing technique in non-sedated infants appears more variable and less repeatable than the equivalent technique during sedation.

Methodological factors that affect variables determined during the raised volume rapid thoracoabdominal compression (RVRTC) technique in infants

(S Stick, S Turner, P Franklin, R Mutch).

We have examined

several methodological differences between existing RVRTC techniques. These include lung volume history determined by peak end expiratory pressure during the breaths immediately preceding the forced expiratory manoeuvre, breath hold prior to expiration and manner of calculating forced expiratory variables. These data will be of value to others using the various RVRTC techniques and for standardisation purposes.

Effects of inhaled glucocorticoid on lung function and exhaled nitric oxide in infants

(S Stick, P Franklin, S Turner, R Mutch).

A double blind, randomised-

controlled study of inhaled Fluticasone Dipropionate is in progress. Outcome measures are lung function using the RVRTC method, exhaled nitric oxide and symptoms. A unique feature of this study is an attempt to recruit infants most likely to have airway inflammation indicated by raised levels of eNO.

Exhaled nitric oxide in infants with respiratory symptoms

(S Stick, P Franklin, S Turner, R Mutch).

Exhaled nitric oxide is raised in infants with recurrent wheeze compared with healthy controls. An interesting observation in a small group of infants with frequent cough without wheeze is a low eNO compared with controls and wheezy infants. Work is continuing to determine whether this is a consequence of disrupted epithelium by whatever is the aetiology of the cough or whether a low NO milieu affects ciliary beat frequency and airway clearance resulting in chronic airway irritation.

Development of Non-Invasive, Partitioned Measurements of Lung Function in Neonates

(J Pillow, Z Hantos, PD Sly)

The development of meaningful,

non-invasive and partitioned measurements of lung function in neonates may provide valuable information for monitoring, optimisation of ventilation and follow-up of infants with respiratory distress in the neonatal period. We have been investigating the potential neonatal clinical applications of the low-frequency forced oscillation technique (FOT) for the last 4 years. We expanded our previous work by specifically examining the effect of administering surfactant at birth to the structurally and functionally premature lamb lung. We observed an effect similar to our earlier observations in preterm lambs exposed antenatally to either steroids or intra-amniotic endotoxin – an effect largely limited to the parenchyma, with a greater reduction in tissue resistance than tissue elastance. The ratio of these two parameters – the hysteresivity – may provide an exciting new measure of the functional integrity of the lung. Work in 2001 will continue to investigate this technique, with a major new collaboration between the ICHR in Perth and Prof. Janet Stocks' laboratory at the ICH in London.

Optimizing High Frequency Oscillatory Ventilation (HFOV) in Neonates

(J Pillow, Z Hantos, R James and PD Sly)

Investigations performed in both

computer and *in vitro* models of the neonatal lung in the preceding four years have shown that the mechanical properties of the lung and the performance characteristics of the ventilators have a strong influence on the magnitude of pressure transmission from the airway opening to the lung

during HFOV in neonates. Work undertaken in 2000 has focused further on defining the optimal conditions for HFOV in the neonate. Using a lamb model and the low frequency forced oscillation technique, we have been able to document the specific changes in lung tissue mechanics with changes in lung volume and how this correlates with oxygen delivery. These studies have given us an exciting new potential measure of determining optimal lung volume during HFOV which is an issue that has vexed neonatal clinicians for some time. Other *in vitro* and mathematical modelling work undertaken in collaboration with the Department of Physics at UWA has also started to examine how the shape of the oscillatory pressure waveform might influence the efficiency of gas exchange, which may in turn impact on iatrogenic lung injury.

Understanding Differences in Delivery of CPAP to Neonates

(J Pillow, R Hagan, L Gurrin, PD Sly)

There have been considerable changes in

the way we deliver continuous positive airway pressure (CPAP) to neonates with respiratory distress, with a particular emphasis on newer methods that reduce the amount of work that a newborn infant has to do while using this mode of respiratory support. We are currently measuring physiological parameters and oesophageal pressures in newborn infants receiving CPAP to determine whether there are significant differences between two newer modes of CPAP (Flow Driver and Bubble CPAP) that might influence their clinical effectiveness. Bubble CPAP is creating a lot of interest world wide, as the pressure waveform has high frequency oscillatory components similar to the frequencies used in HFOV. Future investigations will focus on how transmission of this oscillatory waveform to the lung is influenced by flow, lung mechanics and leak during CPAP in the neonate.

Lung Growth and Development

Intra-uterine inflammation and the fetal lung

(KE Willet, AH Jobe^a, M Ikegami^a, TJ Moss^b, JP Newnham^b, T Quach, R Collins, PD Sly)

^a Children's Hospital Medical Center, Cincinnati, Ohio, USA

^b University Department of Obstetrics and Gynecology, UWA.

Respiratory distress syndrome is a major cause of morbidity and mortality in preterm infants. It results from a combination of extreme surfactant deficiency and structural immaturity. While most infants who develop respiratory distress syndrome will recover, up to 20% will subsequently develop neonatal chronic lung disease. *In utero* inflammation is thought to play an important role in the pathogenesis of neonatal chronic lung disease: high levels of inflammatory markers are seen at birth in preterm infants who subsequently develop neonatal chronic lung disease. Paradoxically there is some evidence that *in utero* inflammation may accelerate fetal lung maturation and reduce the incidence of respiratory distress syndrome. During the past year we have examined the impact of *in utero* inflammation on the developing fetal lamb lung. Endotoxin is found on bacterial cell walls and can be used to stimulate an inflammatory response. We exposed fetal lambs to *in utero* inflammation by administering endotoxin either as a single intra-amniotic injection at 80 days gestation (acute exposure) or as an infusion into the amniotic cavity between 80 and 108 days gestation (chronic exposure). Lambs were delivered 4 weeks prematurely at 125 days gestation. At 125 days gestation the lungs of fetal lambs are similar to the lungs of human infants at around 30 weeks gestation (extremely immature). Both acute and chronic endotoxin exposure led to improved lung function, indicating accelerated functional maturation of the fetal lung. The improvement in lung function was more pronounced in lambs exposed to chronic as opposed to acute *in utero* inflammation. At the time of delivery, inflammatory cells were found in the lungs of both acute and chronically exposed animals, indicating a prolonged fetal inflammatory response. The fetal response to endotoxin appears to be very different to the response seen in adult animals, which subsides by around 72 hours. Inflammation was more marked in chronically exposed than acutely animals, and there was a strong correlation between the improvement in lung function and the level of inflammation. In other words, the fetuses that mounted the greatest inflammatory response showed the greatest improvement in lung function, suggesting that there may be a cause-effect relationship between inflammation and lung maturation. Chronic, but not acute, endotoxin exposure led to a very pronounced decrease in alveolar surface area and an enlargement of peripheral gas exchange structures. These structural abnormalities are consistent with pathologic findings in infants who die from neonatal chronic lung disease. Our findings in preterm lambs suggest that *in utero* inflammation accelerates functional maturation of the fetal lung, but can also cause

profound structural abnormalities. Further studies will examine the mechanisms by which inflammation impacts on structure and function of the developing lung.

Inhaled Glucocorticoids: Effect on long structure and function during the early postnatal period

(J Kovar,
KE Willet,
PD Sly)

This study will ultimately examine the effects of chronic inhaled steroids on alveolar development and lung function in early life, using an animal model. Our efforts this year concentrated on developing a technique for assessing the drug deposition pattern in the lungs of young rabbits. This preliminary study is necessary to test the effectiveness of our aerosolization system for drug exposure. The first step involved the use of an anderson cascade impactor to determine whether a fluorescent label (DiI) has a similar *in vitro* aerosolization and deposition pattern to the drug we plan to use for chronic inhaled steroid exposure (Budesonide). After establishing that Budesonide and DiI have a similar *in vitro* deposition pattern, we exposed 1 and 12 week old rabbits to DiI *in vivo*, to examine the effectiveness of our aerosolization system. We are able to see where in the lungs our aerosol particles are deposited, by examining DiI deposition under a fluorescent microscope. Our results showed that DiI is a safe, reliable and relatively inexpensive marker for Budesonide deposition in rabbit lungs, and offers a good alternative to radioisotopes. The main study protocol, involving chronic inhaled Budesonide exposure, began late in the year and will continue next year.

Cystic Fibrosis

Early detection of inflammation in cystic fibrosis

(S Brennan, K Winfield,
PD Sly)

In 2000 this research group continued investigations in the area of early development of inflammation and infection in cystic fibrosis through a project funded by the NHMRC. This project aims to investigate the following:

1. To characterise the inflammatory response in the lungs of infants and young children with CF and to correlate this with bacteriology, clinical status and lung function.
2. To characterise the ability of products secreted by *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* to

stimulate inflammatory cytokine production by epithelial cells and to determine the ability of various antibiotics to inhibit this process.

3. To establish a mouse model of CF inflammatory lung disease stimulated by bacterial products or infection.
4. To correlate the inflammatory response in the mouse model with lung function measured using a new adaptation of the low frequency forced oscillation technique.

Our findings to date are outlined below:

- Sixty three broncho-alveolar lavage fluid samples have been collected from 39 different children with CF. Inflammation is evident in all of the lavage fluids collected, even in the very young children (less than 3 months of age), with no apparent infection.
- It appears that once acquired, inflammation consistently tracks with infection.
- The level of acquisition of *Staphylococcus* and *Haemophilus* is lower in this cohort than compared with other national CF centres for the same age group. This may be a consequence of the prophylactic antibiotic policy in the WA paediatric clinic. There appears to be no difference in the age of acquisition in *Pseudomonas* in our clinic compared with the other national CF centres.
- Using epithelial cell lines derived from trachea and nasal polyps of patients with CF we have tested a dose range of the sterile supernatants from *Haemophilus*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* and have shown that *Pseudomonas* is the most potent of the three bacteria at inducing an IL-8 response.
- Erythromycin, clarithromycin and roxithromycin have been assessed for their ability to inhibit these inflammatory responses with *Pseudomonas*. We have observed that the nasal polyp cell line produces more IL-8 than the TE cell line following the same stimulation, which may be indicative of either the transformation process or the innate ability of the cells to be stimulated at different levels. We are currently assessing a CF derived bronchial epithelial cell line for responses to the important pathogens in CF.

National Hypotonic Saline Trial

(S Brennan, E Balding)

In 2000, we participated in the co-ordination of a national trial of inhaled hypertonic saline (NHSCF Trial) as an adjunct therapy for CF. This trial was launched nationally in August 2000, and locally in WA in October 2000, and is expected to reach completion in May 2002.

Nasal wash as a tool for assessing inflammation in young children with cystic fibrosis

(PMC Pitrez, S Brennan, PD Sly)

Bronchoalveolar lavage is widely used as a tool for assessing infection and inflammation in children with cystic fibrosis. However, this procedure is invasive and requires general anaesthesia. Nasal secretions are easy to collect and may be a non-invasive way of monitoring airway inflammation. This year we collected nasal secretions from children with cystic fibrosis under 5 years old that were also undergoing bronchoalveolar lavage. We compared the levels of Interleukin-8 (IL-8), one of the important cytokines in CF lung disease, from nasal secretions and from fluid taken from the lower airways and found a positive significant relationship between them. These results indicate that nasal washing might be a simple and useful method to assess lung inflammation in young children with cystic fibrosis.

Pulmonary Pharmacology

Modification of allergic inflammation with bacterial lipopolysaccharide (LPS)

(M Tulic, PD Sly, P Holt)

The prevalence of asthma and allergic sensitisation in developed countries is increasing at an alarming rate. The reasons for this remain unclear. While viral infections are the most common cause of exacerbations in asthmatics, evidence suggests that bacterial-induced infections in childhood may protect against atopy and asthma in later life. The 'hygiene hypothesis' attributes increased disease prevalence to a reduction in overall microbial load in western populations. Currently the effects of bacterial infection on allergic inflammation are poorly understood and the mechanism(s) underlying these effects remains to be explained.

The aim of this study was to: 1. To develop and characterise *in vivo* models of allergic and bacterial inflammation using PVG (Piebald-Virol-Glaxo) rats.

2. To investigate the effect of bacterial inflammation on response to allergen when given a) before primary allergic sensitisation, b) during allergen challenge or c) after allergen exposure in sensitised animals. 3. To examine the role of nitric oxide (NO) and IL-10 as potential mediators in this model.

Results suggest that *in vivo* modification of allergic response by LPS is dependent on the dose and timing of bacterial exposure. Exposure to LPS early in the sensitisation process prevents primary sensitisation and hence the development of allergic inflammation. Exposure to LPS during ovalbumin (OVA) challenge dose-dependently inhibits OVA-induced cellular inflammation and hyperresponsiveness (HR) to Methacholine (MCh) while LPS exposure after OVA challenge further exacerbated neutrophil influx and MVL and returned lung function to normal. In this model, NO production by iNOS contributes to cellular inflammation and microvascular leakage seen 24 h after OVA challenge in sensitised rats. NO produced by nNOS limits bronchial HR to MCh. Therefore, LPS has the ability to modify an established late-phase allergic response by reversing OVA-induced changes in NOS isoenzyme activities and modulating the release of anti-inflammatory IL-10.

Clinical Research Projects

The Family Asthma Study

(PD Sly, RC Mutch, AM Callaghan, GE Kendall)

The Family Asthma Study is part of an international collaborative effort funded by Glaxo Smith Kline investigating the genetic basis of asthma and allergy. Begun in 1999, the work is continuing into the early part of 2001 with the aim to complete testing on 100 families.

Identifying and recruiting eligible families has been one of the most challenging aspects of this study. A family must have an asthma-affected sibling pair, aged between 7 and 35 years, in addition to both genetic parents willing to participate. To date, over eighty families have completed the modified ISAAC questionnaire and formal laboratory measures. Laboratory testing for a family could take up to 4 hours; measures are: weight, height, skin prick testing to 9 common allergens, exhaled nitric oxide, baseline spirometry, the cockcroft methacholine challenge and a blood test.

Individuals and families have made the effort to contact us following study participation, to describe their increased understanding and improved

management of their asthma with additional gains in lifestyle. We acknowledge the generosity, interest and support of all participating families who make this study possible.

Immune response of wheezing in infancy (PMC Pitrez, S Brennan, PD Sly)

We have looked at cells and inflammatory markers in nasal secretions of different groups of wheezing infants associated with respiratory viral infections. We found that neutrophils are the most common inflammatory cells within the upper airways of these patients. It is likely that these granulocytes play an important role in wheezing infants. IL-10, which is an anti-inflammatory cytokine, is increased in the infants during their first episode of wheezing. This finding may explain why some infants are more susceptible to wheezing in early childhood. Further work in 2001 will define these roles more clearly.

Role of early, repeated viral respiratory infections and the development of atopy in childhood (The Childhood Asthma Study) (M Kusel, PD Sly, P Holt, R Loh)

This study, which has recruited 263 children prenatally, has been recording every respiratory infection that the children have been exposed to from birth. To date, 3,000 infectious episodes have been reported and postnasal aspirate/ nasal mucous specimens have been collected for each of these episodes for future analysis.

More than half of the children were found to have eczema at 6 months of age and over a quarter of them had a positive skin prick test to at least one allergen. By the age of 2 years the prevalence of eczema had decreased to thirty three percent but the prevalence of positive skin prick tests had risen to forty four per cent.

At 6 months of age, the most common allergen the children reacted to were egg white and cow's milk, whilst at 2 years, they reacted most often to house dust mite and cat dander. The prevalence of eczema at 3 and 4 years of age has remained steady at a third of the cohort.

The first group of children will be turning 5 years of age in July 2001 and will undergo lung function tests and further skin prick tests.

The level of commitment and support from the families has remained very high with a retention rate of 81 per cent over the period of the study.

The Mucosal Immunity in SIDS Study (M Gleeson¹, R Clancy¹, J Scurlock², P Sly³, A Callaghan³, S Hall¹, G Cooper¹, S Gulliver¹)

¹John Hunter Hospital, ²Princess Margaret Hospital for Children, ³Institute for Child Health Research

The Institute for Child Health Research and Princess Margaret Hospital for Children contributed to a research project conducted by John Hunter Children's Hospital in New South Wales. This study aimed to investigate if children presenting with acute life threatening episodes of unknown origin (ALTEs) are associated with a disturbed mucosal immune response from an underlying infection or inflammatory stimulus. Four groups of infants were enrolled in the study: well infants; infants experiencing mild upper respiratory tract infection; infants admitted to hospital with an ALTE; and later in the study, infants presenting with bronchiolitis. Two saliva samples were collected, the first at presentation and then another fourteen days later. In the Western Australian arm of the project, only those infants presenting with ALTE participated in the study. Statistical analysis is being carried out on this data. We feel further studies are probably indicated especially with younger children.

The researchers would like to thank the families for their kind contribution, and in particular, acknowledge those families who had very sick infants at the time of the study.

Vaccine Trials

(P Sly, R Loh, D Mallon, P Richmond, B King, J Harvey, M Pradhan, M Trainor, M Odam, M Wright, T Nielsen, K White, R De Leuil)

The Vaccine Trials Group performs Phase 1, 2 and 3 trials with new vaccines, trials of non-vaccine treatments for vaccine preventable diseases and conducts research into the development of immunity to vaccines and vaccine preventable diseases. This year we relocated to our new premises in the Children's Clinical Research Facility and we have expanded to include allergy treatments and adult studies. Our group is also collaborating with Professor Pat Holt's Cell Biology Laboratory to examine the cell mediated response to vaccines and the effect of vaccines on the developing immune system. We are continuing to develop our links to the community by providing information regarding immunisation to health professionals and members of the public.

Several international studies continued or

commenced in 2000. These included:

A Parainfluenza type 3 (PIV-3) vaccine study, phase II, multi-centre, double-blind, randomised, placebo controlled study of the safety and immunogenicity of PIV-3 live, attenuated, parainfluenza type 3 vaccine in healthy children 6-18 months of age.

A respiratory syncytial virus/parainfluenza type 3 (RSV/PIV3) vaccine study, phase I study of the safety, tolerability, viral shedding profile and immunogenicity of a live, attenuated combination RSV/PIV3 vaccine in 6-18 month old seronegative children.

Pneumococcal vaccine study, phase III randomised study to compare the safety and immunogenicity of three unique lots of the 9-valent pneumococcal capsular polysaccharide-CRM197 conjugate vaccine in healthy infants.

Measles/Mumps/Rubella/Varicella (MMR-V) vaccine study, phase III, randomised, controlled primary vaccination study to assess the consistency of 3 production lots of a combined MMR-V vaccine in terms of immunogenicity and safety, compared to the administration of measles/mumps/rubella and varicella (either concomitantly or 6 weeks apart) in healthy children in their second year of life.

Respiratory Syncytial Virus (RSV) vaccine study, phase I multicentre study of the safety, tolerability, viral shedding profile, and immunogenicity of a recombinant, live, attenuated RSV subgroup a strain virus in adults, RSV seropositive 15-59 month old children and RSV susceptible 4-24 month old infants.

Influenza vaccine study, randomised, double-blind, compared, controlled, phase II study in 242 subjects aged 60-85 years inclusive receiving either the thiomersal-free vaccine or the reference (thiomersal containing) influenza vaccine.

Seasonal allergic rhinitis treatment study, double-blind, randomised, placebo controlled, parallel group study assessing the efficacy and safety of oral fexofenadine HCL 30 mg tablets twice a day in 6-11 year old subjects with allergic rhinitis.

Staff and Students

Head of Division

Peter D Sly MD FRACP

Professorial Fellow, Department of Paediatrics, The University of Western Australia

Research Staff

Cindy Bailey RN

Siobhain Brennan *PhD*

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Rachel Collins *BSc(Hons)*

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PGradDip(HlthAdmin) MSc(Addiction) PhD
candidate*

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Raewyn Mutch *MBChB DipRACOG FRACP PhD
candidate*

Denise Stapleton *BAppSc PhD candidate*

Meri Tulic *BSc(Hons) PhD candidate*

Visiting Research Scientists

Paulo Pitrez

Awards

R Collins. Boehringer Ingelheim Best Poster Award, TSANZ 2000, \$500

J Kovar. Australian Lung Foundation Travel Award

J Kovar. University of Western Australia Graduates Association Postgraduate Travel Award

R Mutch. TSANZ Travel Grant 2000.

R Mutch. UWA Amy and Athelston Saw Medical and Dental PhD Scholarship

R Mutch. PMH Postgraduate Clinical Association Travel Grant

J Pillow. Neil Hamilton Fairley Fellowship for 2001-2004.

MK Tulic. Angel Ludwig Post Doctoral Fellowship 2000.

MK Tulic. Karolinska Post Doctoral Fellowship (declined).

MK Tulic. TSANZ/Allen & Hanbury's New Investigator Award 2000.

MK Tulic. TSANZ Travel Grant 2000.

Theses Passed

Graham Hall *PhD* University of Western Australia, 2000. Estimation of the mechanical properties of the airways and respiratory tissues in infants using low frequency forced oscillations.

Jane Pillow *PhD* University of Western Australia, 2000. Optimizing high-frequency oscillatory ventilation for neonates. Awarded with Distinction.

External Committees

PD Sly. Joint American Thoracic Society - European Respiratory Society Task Force on Standards for Infant Respiratory Function Tests (1997-).

PD Sly. Asthma Consultative Group, Australian Lung Foundation (1999-).

PD Sly. Executive Committee, Australasia Paediatric Respiratory Group (1999-2000).

PD Sly. Central Programming Committee, Thoracic Society of Australia and New Zealand (1997-2000)

PD Sly. Asthma Foundation of Western Australia Research Sub-Committee Chairman (1998-)

PD Sly. Asthma Foundation of Western Australia Medical Advisory Committee (1991-)

PD Sly. Human Ethics Committee, Princess Margaret Hospital for Children (1991-)

PD Sly. Human Ethics Committee, Scientific Advisory Sub-Committee Chairman, Princess Margaret Hospital for Children (1993-)

Invited Presentations

J Pillow. Draegar Ventilation Symposium – PSANZ Meeting (Brisbane, March 2000): Lung Mechanics and Frequency – Understanding the Pressure Costs of Ventilation.

J Pillow. Kerttu & Kikke Valle Paediatric Pulmonology Symposium (September 2000): Lung Mechanics and Frequency – The Third Dimension.

PD Sly. Parenchyma – Effects of posture, growth and sleep. 6th World Congress on Sleep Apnea. Sydney, March 2000.

PD Sly. Infants on ventilatory support. 4th International Congress on Paediatric Pulmonology. Nice, February 2000.

PD Sly. Mechanisms and Triggers of Asthma. Environmental Threats to the Health of Children Conference. Manila, 2000.

PD Sly. Flow Volume Underworld Workshop, Villa Pomela, Italy September 2000.

Institute Nurses Network

The Institute Nurses' Network (INN) is an initiative of nurses within the Institute to improve child and family health by utilising the unique knowledge and skills of nurses in research. INN was established in September 1997 as a forum for nurses to discuss issues related to nursing practice in research.

The aims of the group are to conduct high quality research, to promote nursing research, to support research nurses within the Institute and in the wider community, to apply research findings to improve the health of children, adolescents and their families, and to be an advocate for the child and for research.

An important activity in 2000 was our collaboration with community child health, generalist, and paediatric nurses, and the Joanna Briggs Institute for Evidence Based Nursing and Midwifery (JBCEBNM) to conduct a Systematic Review of research on pacifier non-nutritive sucking in infancy and early childhood. A protocol has been developed and application for funding has been made. It is envisaged this project will be completed in 2001.

Committee members:

Ann Callaghan, Garth Kendall and Anne Mahony

Division of Molecular Biology

Wayne Thomas



Overview

A number of very significant developments have occurred in molecular studies of house dust mite allergens. Our analysis of the genetic drift of house dust mite allergens in homes in Australia and Taiwan found that the two major allergens have a limited pattern of diversity and this diversity was the same in both geographical areas. This provides a practical and rational basis for formulating recombinant mite allergens to represent the allergens encountered in the environment rather than relying on the undefined genetic make up of mites used to prepare the current commercial extracts. As well as the problem of genetic variation our previous work also found that the allergen extracts lacked important allergens. It was not known if the missing allergens were only produced in small quantity by the mite and were very potent or if the extracts were simply inappropriate. Work in collaboration with Dr Tovey at the Institute for Respiratory Medicine in Sydney has now shown that one of the “missing allergens”, Der p 7, is present in copious quantities in inhaled air. Our work with recombinant allergens and monoclonal antibodies is thus inexorably redefining the knowledge of the triggers of mite allergy and asthma. A major new concept being investigated is the existence of regulatory specificities where some allergens which include Der p 7 and Der p 14, induce large protective Th1 responses in non-allergic people in contrast to the allergens Der p 1 and 2, which induce similar Th1 responses in both allergic and non allergic people. Since both Der p 7 and 14 are unstable in extracts the proposed regulatory function has only been revealed by our studies with recombinant allergens. It may, by using recombinant allergens, be possible to harness the regulatory activity of Der p 7 and 14 for desensitisation treatment.

Recognition of the earliest allergens which induce sensitisation is an important element in the study and treatment of mite allergy in children. Our studies have shown that cells in the cord blood respond best to the major allergens Der p 1 and Der p 2 consistent with the intriguing work of others on prenatal sensitisation. An intriguing new development has been the discovery of the cord-specific epitope(s) found in peptide 20-38 of Der p 1, a specificity which stimulates cord T cells at high frequency and induces the T-cell cytokine IL-5. Adult peripheral blood cells do not respond to this epitope. It therefore provides a marker for cord cell responses and the reason for the loss of the response which may be related to cross reacting food or self antigens, poses a significant question in the development of the immunological repertoire.

New endeavours to perform a more complete study of cat allergens and to represent the shape of allergens with peptide mimics have made considerable progress.

House Dust Mite Allergens

Genetic variation of allergens from homes in Perth and Taiwan

W Smith,
LA Hazell,
WR Thomas

Sequences from the house dust mite allergens Der p 1 and Der p 2 from individual homes in the Perth metropolitan area were obtained by RT-PCR of small samples of mites. The Der p 2 sequences were compared with similar sequences previously obtained from Taipei. A pattern of genetic divergence to two distinct sequences was found with the most abundant sequence, Der p 2.0101 (in 50% of mites), evolving to the sequence Der p 2.0104 with 4 key amino acid variations at positions 40, 47, 111 and 114. Significantly Der p 2.0104 sequences from both regions also shared the same pattern of non-coding nucleotide changes pointing to a common origin. The Der p 1 sequence variation followed previous findings with only one consistent substitution at position 124 and a series of sporadic changes each occurring infrequently and in the absence of non-coding changes. It thus appears that the bulk of Der p 1 and Der p 2 allergens can be represented with 2 sequences of each allergen which will simplify the development of new therapies based on recombinant allergens or synthetic peptides.

T-cell responses to recombinant Der p 2 variants

BJ Hales, W Smith,
LA Hazell, A Jarnicki,
WR Thomas

Studies with the group 1 mite allergens have shown that changes in the sequence due to allelic polymorphism or intra-species variation can markedly affect T-cell responses of peripheral blood mononuclear cell preparations. Parallel studies with affinity purified natural allergens from *Dermatophagoides pteronyssinus* and *D. farinae* however found that the Dp and Df allergens elicited very similar proliferative and cytokine responses despite an 80% sequence divergence. It therefore appeared that T-cell responses to whole allergens are less affected by sequence variation than the responses to individual peptides, which is important information for new types of immunotherapy. To test this in a defined manner, recombinant proteins representing the variants of Der p 2 allergens were produced in *Escherichia coli* and refolded, a procedure which produced protein suitable for X-ray crystallography. T-cell stimulation tests, as measured by proliferation, showed a broad concordance in the responses to each variant and people had either low or high responses to Der p 2 as measured with any

variant (figure 1). The Der p 2.0104 variant which is the most divergent from the most abundant Der p 2.0101 variant was however the lowest stimulator for almost all subjects, and the variant Der p 2.0107 with only a single N-terminal substitution was frequently the highest. It is therefore possible that these consistent changes could affect the efficacy of allergen therapy and further studies are being conducted with cytokines and different allergen preparations.

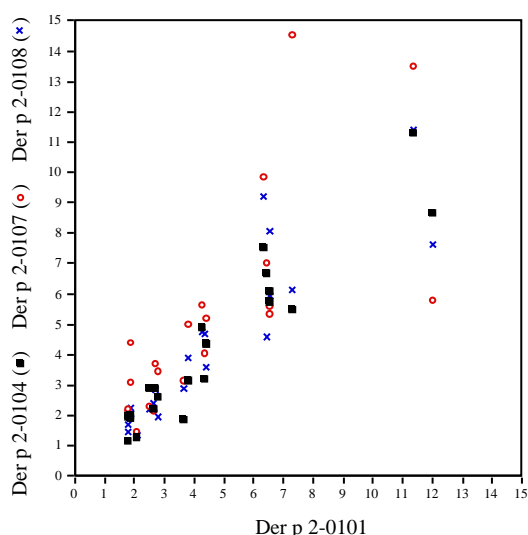


Figure 1. Proliferative responses of PBMCs to polymorphic variants of Der p 2.

PBMCs from 21 subjects were stimulated with recombinant variants of Der p 2.0101, 2.0107, 2.0107, and 2.0108. The mean stimulation indices of the responses of each individual to Der p 2.0104, 2.0107 and 2.0108 are shown plotted against their response to Der p 2.0101 as a reference. The correlation coefficients versus Der p 2.0101 were 0.94, 0.73 and 0.89, respectively, for 2.0104, 2.0107, and 2.0108.

Two Der p 4 amylase genes

KL Mills, WR Thomas,
W Smith

The allergen Der p 4 which is an alpha amylase was produced as a recombinant protein in the yeast *Pichia pastoris* and shown to be a highly active enzyme. The IgE binding activity was however lower than that anticipated from reports of immunochemical studies performed with substrate-purified protein. To investigate the possibility that different alpha amylases are produced by house dust mites, a genomic DNA library of *D. pteronyssinus* was constructed in a lambda vector and screened for homologous amylase sequences. As found for other organisms, *D. pteronyssinus* contains two adjacent

genes for alpha amylase which had 70% sequence identity. This contrasts with the 90% identity found between the amylase sequences isolated from the *D. pteronyssinus* and *Euroglyphus maynei* mite cDNA libraries. The second amylase gene was however unusual in that it had a short signal sequence. It was however transcribed by the house dust mite because cDNA could be produced by RT-PCR of wild mites. Experiments to produce the recombinant second gene and examine IgE binding and T-cell reactivity are in progress.

Cord blood epitopes

N Malainual, BJ Hales, WR Thomas with BJ Holt and PG Holt, Cell Biology Division

Cord blood T cells can be stimulated to proliferate with proteins commonly encountered in the environment but not other proteins such tetanus toxoid. To analyse the specificity of the response, cord blood cells were stimulated with a series of overlapping peptides of Der p 1 and shown to respond at high frequency to a region known to induce the most frequent responses in adult peripheral blood mononuclear cells. In addition however they responded almost as frequently, and to the same degree, with an epitope or epitopes in a peptides containing residues 20-38. Since adults were not known to respond to this peptide confirmatory studies were conducted and indeed 70% of cord responders to Der p 1 are stimulated with the peptide compared to 0% in adults. Moreover the cord cells can be induced to produce the T cell cytokine IL-5. It thus appears to be a cord specific response and thus precludes the cord responses being due to contamination with maternal cells. An interesting aspect of this peptide which may relate to the unresponsiveness of adults is that 15/19 residues are invariant across a range of cysteine proteases which includes Der p 1 and even human cathepsins (figure 2). The responses of adults could therefore be modified by the ingestion of food or by self tolerance. Studies on the epitope specificity and cell markers are continuing.

DER P1	R	T	V	T	P	I	R	M	Q	G	-	G	C	G	S	C	V	A	F	S	
HUMAN	G	Y	V	T	P	V	K	N	Q	G	-	Q	C	G	S	C	V	A	F	S	
COFF	G	Y	V	T	P	V	K	N	Q	G	-	Q	C	G	S	C	V	A	F	S	
CHICKEN	G	Y	V	T	P	V	K	D	Q	G	-	Q	C	G	S	C	V	A	F	S	
RICE	G	R	V	A	E	I	K	D	Q	G	-	G	C	G	S	C	V	A	F	S	
WHEAT	K	V	V	T	P	V	K	N	Q	G	-	K	V	C	G	A	C	V	A	F	S
BEAN	G	A	V	T	P	V	K	D	Q	G	-	S	C	G	S	C	V	A	F	S	
PAPAIN	A	V	V	T	P	V	R	M	Q	G	-	G	C	G	S	C	V	A	F	S	
	G		V	T	P	V	K		Q	G			C	G	S	C	V	A	F	S	

Figure 2. Conservation of cord-specific epitope (p20-38)

Cloning of mite allergens and antigens with different effector and regulatory functions

MJ Epton, BJ Hales W Smith, N Malainual, WR Thomas

The ability of the newly described lipid-binding allergen Der p 14 to elicit cytokine from peripheral blood mononuclear cells was compared to that of the known major allergen Der p 2 and mite ferritin, a protein for which little evidence of allergenicity could be shown. The Der p 14 is of particular interest because it is a high molecular weight lipid apolipoprotein or vitellogenin-like protein found either in lipid bodies or eggs. Although evidence for a high IgE binding activity of group 14 allergens has been published the protein degrades rapidly in extracts. The recombinant Der p 14 used was a 200 amino acid C-terminal fragment of the 1650 amino acid protein since this could be produced in a soluble form as refolded polypeptide from inclusion bodies of *Escherichia coli*. The ferritin (apoferritin light chain) was produced by the same method. All three proteins were highly antigenic as determined by proliferation assays and the responses of mite-allergic people to Der p 2 and 14 were marked by high levels of Th2 cytokines. The difference between responses to Der p 2 and 14 was found in non-allergic people where Der p 14 induced much higher levels of the Th1 cytokine interferon- γ . This is similar to responses to Der p 7 and it is speculated that they may be key regulators to direct immunity away from allergy. The responses to the non-allergenic ferritin were also very high but had mixed responses of Th1 and Th2 cytokine which did not differ with allergic status. Different allergens thus elicit different cytokine patterns which may govern different aspects of allergic sensitisation.

Allergens in inhaled air

WR Thomas, BJ Hales, KL Mills, W Smith with ER Tovey Institute of Respiratory Medicine, Sydney and HD Shen Veterans General Hospital, Taipei

Allergens such as Der p 7 and 14 induce strong T-cell responses but are found in very low concentrations in extracts. While people are highly sensitised to the allergens, they may not induce disease if exposure is low. The recent development of filters to capture air inhaled into the nose and the application of sensitive immunostaining techniques has provided a method to detect allergen on small particles in inhaled air. A project to produce monoclonal antibodies to the different mite allergens to use for detection has commenced. The first results with anti Der p 7 antibodies conducted at the

Institute of Respiratory Medicine show that this allergen is present in inhaled air in the same amount as the major allergen Der p 1 despite a 1-200 fold difference in abundance in extracts. The high level of sensitivity to this allergen is therefore consistent with a high environmental exposure.

Peptide epitopes inhibit Th2 cytokine production during respiratory sensitisation

AG Jarnicki,
WR Thomas with
T Tsuji, Fujita
Health University,
Aichi Japan

Peptides containing the major T-cell epitopes of the allergen Der p 1 can, when administered intranasally, inhibit immune responses to the injection of the allergen Der p 1. Responses to antigens delivered to the mucosal are however regulated differently to those induced by injections and could also be affected by local inflammation produced by the intranasal peptide itself. We have measured responses of mice sensitised by the intranasal administration of Der p 1 in conjunction with a mutated *E. coli* enterotoxin adjuvant. The administration of intranasal peptide even at the high amount of 5 daily doses of 100 micrograms did not decrease IgE antibody production or IgG1 and IgG2a. It did however reduce the production of the cytokines IL-4 and IL-13 by 50% while not affecting IL-2, IL-5, IL-10 or interferon- γ . This pattern of cytokine regulation is different to that found for the injection protocol where IL-2 is highly sensitive, and it does not implicate a role for the regulatory effects of IL-10, which is often increased in injection models. Besides helping IgE production the cytokines IL-4 and IL-13 have other direct effects on cell infiltration, activation and mucous production which could be reduced by the treatment.

Direct respiratory sensitisation to birch and papaya allergens

AG Jarnicki,
WR Thomas with
PG Holt, Division of
Cell Biology

The allergens Bet v 1 and papain from papaya are potent respiratory allergens. Papain a homologue of the Der p 1 allergen of mites is being studied because it can be purchased in the large quantities required for comprehensive investigations of respiratory sensitisation. Bet v 1 is being examined because mutated hypoallergenic recombinant allergens are available from other laboratories. A study of different regimens of papain inhalation failed to reveal a protocol which induced predictable

sensitisation but instead confirmed the overriding phenomenon of inhalation tolerance. Prolonged sensitisation could be achieved by the administration of papain or Bet v 1 with a mutated *E. coli* enterotoxin adjuvant but although this had sustained IgE production the lung inflammatory response was primarily monocytic. A bystander regimen was therefore devised where mice were first sensitised by an intraperitoneal injection of albumin in alum and then after 2 weeks exposed to intranasal installations of Bet v 1 or aerosols of papain mixed with albumin. Both groups developed sustained levels of IgE production which for papain reached high titres and persisted after repeated cycle of exposure. On challenge the mice produced highly eosinophilic lung infiltrates. The responses to the bystander antigen thus permitted the induction of sensitisation instead of tolerance. Interestingly, the albumin itself failed to induce IgE titres suggesting that IL-4 may not be a key ingredient of the bystander stimulating activity. Although even high doses of papain inhalation did not induce persistent IgE responses, the intranasal administration of papain did and primed for boostable responses to inhalation. This could be achieved with either high doses or a larger number of low doses. Intermediate doses were interestingly inhibitory. The experiments have thus developed model systems which achieve respiratory sensitisation without the injection of the test antigen. These will be studied for desensitisation and for interactions which occur during sensitisation to complex mixtures of allergens.

Mimotopes of the Der p 1 allergen

SR Gunn, WR Thomas with
PM Watt, Division of
Leukaemia and Childhood
Cancer

Mimotopes are peptides which adopt a shape that mimics the antibody-binding epitopes including complex conformational epitopes. They are potentially useful because a small peptide mimotope, mimicking a single epitope, could be a potential allergen vaccine which will not cross link IgE and induce anaphylactic reactions. A monoclonal anti Der p 1 antibody has been used to isolate mimotopes from peptides expressed in phage display libraries using a late affinity purification method. Phage from libraries constructed to express the peptide on the pIII or pVIII proteins have been enriched by 3 cycles of purification and then panels of enriched phage grown and analysed by ELISA against the monoclonal antibody and a control antibody of another specificity. The ELISA test system was validated by constructing phage expressing a known

Bet v 1 mimotope to the BIP monoclonal antibody. About 20 % of the enriched clones showed specific positive reactions. Positives clones from the pIII libraries were sequenced and 12 had the same sequence while 2 others were different but had a similar consensus sequence. Optimisation of these protocols is currently underway as well immunisation experiments to produce anti-allergen antibodies.

Cat allergens

W Smith, AJ Butler,
WR Thomas with MD
Chapman, Center for Allergy and Asthma,
Charlottesville, Virginia

There are several reasons, including cross reactivity with other animals, to suspect that cats produce several potent allergens other than the much-studied Fel d 1. Given that cat allergy has been, and is being used as prototype for new desensitising strategies in clinical trials there is an urgent need to examine other potential allergens. A panel of sera from cat allergic people has been collected and screened against serum and extracts of dander, skin, liver and anal and salivary glands. A number of reactive bands were observed which varied with the tissue and surprisingly few were attributable to Fel d 1. cDNA libraries were constructed from skin, liver, parotid and mandibular glands and the anal library is in progress. Screening of the liver with IgE radioimmune assay has resulted in the isolation of IgE binding clones which are neither Fel d 1, albumin nor cystatin, the only hitherto described IgE binding proteins.

External Committees

WR Thomas. Deputy Chairman, NHMRC Discipline Panel of Inflammation, Allergy and Haematology.

WR Thomas. Chairman, International Union of Immunological Societies/WHO Allergen Nomenclature Committee.

WR Thomas. Member, International Review Panel for Joint Research Program. Austrian Science Fund.

WR Thomas. Co-chairman, Working Group and Position Statement on Indoor Allergens. World Allergen Organisation.

WR Thomas. Member, Asthma Foundation of Western Australia Executive Committee.

Invited Presentations

WR Thomas. Recombinant allergens. New diagnostic and therapeutic products. Seminar. American Academy Allergy Asthma and Immunology, San Diego, USA.

WR Thomas. Lipid binding apolipoprotein contains major IgE binding specificities. Selected plenary speaker, Collegium Internationale Allergologicum, Hakone, Japan.

WR Thomas. Hierarchy for allergenicity, symposium, XVII International Congress of allergology and clinical immunology, Sydney.

Staff and Students

Head of Division

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Professor (The University of Western Australia)

Research Staff

Amanda J Butler *BSc Hons*
Belinda J Hales *BSc Hons PhD*
Lee A Hazell *Dip Appl Sci*
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Stephanie R Gunn *BSc Hons PhD candidate joint Children's Leukaemia and Cancer*
Andrew G Jarnicki *BSc Hons PhD candidate*
Nat Malainual *BSc MSc PhD candidate*
Kristina L Mills *BSc Hons PhD candidate*

Division of Population Sciences

Associate Professor
Stephen Zubrick



Overview

The Division of Population Sciences has seen the completion of its inaugural year of work in the new Institute building. For the first time since the Institute started its work, researchers and students have been housed together in one building and in areas specifically designed for the many research groups and projects that comprise Population Sciences. Populations are, of course, diverse and complex and these characteristics are reflected in the many differing research projects and studies undertaken within this Division. The diversity and complexity of population research can be seen in some of the questions our researchers and their teams seek to answer. For example: what is the prevalence and incidence of perinatal, infant and child mortality and what are the underlying associations and causal mechanisms? What is the ongoing occurrence of preventable diseases such as neural tube defects and how can we advance their prevention? What happens between birth and age 5 to infants born with neonatal encephalopathy – how well do these children develop and manage when compared to normal infants? Does the introduction of public swimming pools in remote Aboriginal communities result in health benefits to children – particularly with respect to the occurrence of otitis media? What are the optimal statistical models and procedures for analysing correlated data and genetic information? Can hearing loss in newborn infants be better detected prior to 6 months of age to allow early intervention? What is the current prevalence of mental health conditions in Aboriginal children under the age of 18 years? What are the causal pathways that lead to significant mental health problems in children followed from early gestation to age 11 years? These are a few of the questions being addressed through research in the Division of Population Science.

The techniques used to examine these questions are as diverse as the questions themselves. Our researchers use methods such as “classic” epidemiological analyses of data held at the Institute in its population registers. Case-control and cohort studies are used. Where necessary, large scale random samples within the community are drawn and trained interviewers collect vital, health and social information from participants. Special attention is given to the development of biostatistical approaches suitable for answering complex questions involving causal associations and underlying genetic variation. Many collaborations are necessary to achieve scientific results and these span, state, national and international borders. What unifies the diversity of our research is its focus on burdensome health conditions affecting mothers, infants, children and families. The goal of this research is both to identify the causal pathways leading to these conditions enabling a scientific approach to prevention where ever possible, and otherwise to identify the best strategies to reduce the burden of poor health on individuals, families and communities.

The many projects and their staff are described on the following pages.

Western Australian Aboriginal Child Health Survey

*SR Zubrick, S Eades,
SR Silburn, AW Read
and D McAullay*

The first fully representative community survey of Aboriginal child health and wellbeing has been underway throughout Western Australia since May 2000. The project is being conducted under the auspices of the Kulunga Research and Training Network with funding from Healthway, the WA Lotteries Commission, the Australian Bureau of Statistics, and several State and Commonwealth Departments. Rio Tinto Mining Corporation has also provided funding to assist the Institute in meeting its commitment to employ and train more Aboriginal staff on the project.

By December 2000 household interviews had been completed with 1,008 families gathering information on 2,644 children of Aboriginal or Torres Strait Island origin.

The survey process is being well received and supported by families with Indigenous children and the estimated participation rate is 89% - that is, 1008 out of 1128 eligible families have so far consented to be enrolled in the study. To gather this amount of information has meant training 120 field staff of whom almost 60% are Aboriginal. Family consent has also been obtained for the survey team to gather information on children in the survey currently enrolled in school. Information on 1,811 of these children has been sought from teachers in some 235 Western Australian schools.

It was originally anticipated that the household interview phase of the study would have been completed by the end of 2000. However a smaller than expected number of families with Aboriginal children was located in the 360 census districts in the census districts originally selected for the study. To address this shortfall, the Australian Bureau of Statistics has selected a further 411 census districts to be searched and surveyed from March to June 2001. To enable this the ABS has agreed to extend its services to the project for a further six months and additional funding is being sought from the projects major State and Commonwealth sponsors. This will require the recruiting and training of a further 55 field staff in February 2001. The school's follow-up of the additional children ascertained in 2001 is expected to continue through to October 2001.

The next phase of the project includes data analysis which will be ongoing through 2002. A clinical and cultural validation study will also be conducted with a sub-sample of approximately 260 of the children stratified on the basis of their mental health status as determined by the screening instruments used in the

survey. The survey results will first be communicated to participating Aboriginal communities in a culturally appropriate form with the assistance of the project's Aboriginal Steering Committee and the Kulunga Research and Training Network. The findings will then be published as a high quality monograph to provide an epidemiological framework not previously available as a planning resource to define the burden and impact of common child disorders at the population and regional levels. This information will assist policy makers, service planners and purchasers in health, education, family & children's services and justice in estimating service needs and the potential advantages of alternate policies and programs.

An evaluation of the effectiveness of a public health program to prevent conduct disorder

*SR Silburn,
SR Zubrick,
KA Northey,
J Smith (Family
Law Court of*

WA), DJ Robertson, A Williams

Researchers in the Division of Population Sciences are examining the feasibility and effectiveness of a population level application of the Positive Parenting Program (Sanders & Markie-Dadds, 1994) in reducing both the prevalence of childhood disruptive behaviour disorder and family risk factors for these problems in both the short and the long term. The program was adapted to a group format and applied as a universal prevention strategy through primary health care services to families with pre-school children aged between 36 and 58 months within areas of high socio-economic disadvantage. A comparison group from a region with similar characteristics is also being studied. Both groups are being followed over a three and a half year period to their entry in Year 1 of school when teachers will be asked to assess their behaviour.

Previous research (Sanders, 1994) has shown that key risk factors for subsequent mental health morbidity include dysfunctional parenting style, parental depression and marital conflict. We hypothesise that the parents of children who participate in Triple P will exhibit lower levels of aversive parenting, greater levels of positive parent behaviour and report higher levels of parenting competence, lower levels of depression, anxiety and stress, and marital conflict than the parents of children who do not receive the Triple P program. Additionally, the children in the former group should show less disruptive behaviour, improved social competence, and lower levels of clinically significant mental health problems.

Our data analytic strategy is presently designed to take account of the differences between the comparison and intervention groups at the outset of the intervention. In order to separate the preventive from the possible interventional effects, our large samples (comprised of both intervention and comparison groups) have been stratified by the clinical status of the child at the start of the intervention (*ie.* those with and without clinically significant behavioural disturbance). For each strata, a series of multiple linear regression analyses have been constructed with the continuous dependent variables of childhood behaviour problems. Each analysis has been adjusted for differences in the intervention and comparison groups at the time of pre-intervention.

Our current analysis shows that Triple P has a preventive effect in that fewer children without behaviour problems develop them subsequent to Triple P. Where children have clinically significant behaviour problems, Triple P provides a short to medium term reduction in these problems. Overall, the Triple P Program was shown to be effective in preventing the development of dysfunctional parenting styles (laxness and verbosity) in the clinic and non-clinic group, and this preventive effect was maintained at 12 and 24 months post-intervention. The program was also effective in preventing the development of over-reactive parenting styles in the non-clinic but not the clinic group. Clinic range children from either a sole parent or step/blended family fared worse than children from original families.

Results from this study are currently being prepared for publication.

**RASCALS Study
(formerly known as
the Western Australian
Pregnancy and Infancy
follow-up Survey)**

SR Zubrick,
SR Silburn,
JJ Kurinczuk
(University of
Leicester, UK),
DE Parsons,

MD Biggs, K Moore, K Dixon, PR Burton
(University of Leicester), in collaboration with VP
Dawes (formerly the Health Department of Western
Australia), AJ Plant (Curtin University).

In 1995 to 1997 we surveyed a 10% random sample of recently delivered Western Australian mothers. We collected the data using a self-completion questionnaire posted out at 12 weeks post-partum. The response was 82%. We have used the result of the study to investigate health related behaviours and events during pregnancy and infancy. Analysis of this rich data source continues.

With two further grants from Healthway we have been able to build upon the data collected in the original survey. For each of the 1995 and 1996 birth cohorts, a random sample of 1,400 women who responded to the original post-partum survey were followed up when their child reached the ages of 13 months, two, three, four and five years of age. The ongoing follow-up continues. This will allow us to elucidate the complex causal chain of events from infancy and early childhood that lead to mental health problems by age eight years and allow us to identify factors that are protective and lead to resilience in the face of adversity. Most importantly we aim to identify within these causal pathways points on the pathway, preferably early points, which are amenable to preventive strategies.

**Western Australian
Pregnancy Cohort
(Raine) Study**

GE Kendall,
LF Clohessy, SJ Hoey,
RL Austin,
KL Moonen,

CM Smargiassi, KV Blake, WH Oddy, FJ Stanley in
collaboration with PD Sly (Clinical Sciences),
PG Holt (Cell Biology), and SR Zubrick and
SR Silburn (Population Sciences)

Approximately 3000 women in early pregnancy were enrolled in this collaborative study between the Institute, The Women and Infants Research Foundation, and the University Department of Paediatrics. Periodic assessments of the children have been carried out at the ages of 1, 2, 3, 5 1/2 and 8 years. Exposure to environmental allergens in early life and the subsequent development of childhood asthma is being examined, as well as the relationship between cough and wheeze in the first year of life and asthma in later childhood. The role of intrauterine growth as an antecedent of the variability in blood pressure in childhood is another focus of the study and the investigators hope to further elucidate other antecedents of blood pressure variability such as body mass index and familial tendency. As a source of measures of intrauterine growth, the pregnancy and newborn data of this study are exceptional. They enable the estimation of several independent measures, both of the adequacy of intrauterine growth and the timing (serial ultrasound measurements) or approximate timing (newborn morphology) of growth failure in cases in which this has occurred. Data are presently being collected at the age of 10 years will be combined with this existing information on fetal growth and development to explore the relationship between intrauterine growth, psychosocial environments and mental health outcomes in childhood such as anxiety disorder and conduct disorder.

Health Department of Western Australia General Purchasing Contract

In October 2000, the TVW Telethon Institute for Child Health Research (ICHR) and the

Health Department of Western Australia (HDWA) formalized their collaborative partnership with the signing of a contract for the provision of maternal, child and youth health services. The contract that is anticipated to run for 3 to 5 years specifies six service areas (A-F) in which ICHR is committed to delivering good quality outcomes.

The contract specifies maternal, child and youth health projects related to child health survey question development, data monitoring and surveillance systems, rural health, briefings and information provision and evaluation of child health programs.

The Contract Team consists of Dr Steve Zubrick, Dr Sven Silburn, Anwen Williams, David Vicary, Kim Clark and Tanyana Jackiewicz. David, Kim and Tanyana have been recruited specifically to ensure the efficient and timely delivery of contract outputs. Tanyana Jackiewicz is responsible for coordinating the contract, while David and Kim are responsible for specific service areas.

Service A of the contract relates to question development for indicators of child health and wellbeing. This part of the contract sees the ICHR delivering specific outputs relating to the development of questions to be included in future surveys of the Western Australian population (*ie.* WA Child Health Survey and the Historic Omnibus Survey). These questions relate to specific indicators for the health and wellbeing of Western Australia's children and youth. A six-monthly progress report on the development of these indicators and subsequent survey question development has been completed and forwarded to the HDWA. This discussion paper included a summary list of recommended indicators for health and wellbeing of Western Australia's children and youth and a preliminary list of suitable survey questions relevant to these indicators.

Service B of the contract relates to monitoring and surveillance of maternal and child health. This service area combines a number of important disciplines including monitoring and surveillance systems, information technology, database management and development, and data linkages. The ICHR is in the process of developing a plan to inform the long term development of monitoring and surveillance systems for maternal, child and youth health in Western Australia.

Service C of the contract is the rural health component. This area of the contract has enormous potential to usefully contribute to the delivery of

health care to rural areas of WA.

Service D relates to briefing sessions and the provision of information to the HDWA. Professor Fiona Stanley gave a briefing to 23 HDWA staff on "The Developmental Health of Children: Opportunities, Partnerships and Directions". Feedback from those who attended was positive.

Service E of the contract relates to the provision of information to assist the HDWA in their purchasing decisions.

Service F of the contract is the evaluation by the Institute of the HDWA's Building Blocks program and the New Vision for Community Health. David Vicary has been recruited to manage this part of the contract. The Institute is pleased to be associated with the Building Blocks program and New Vision for Community Health. ICHR has the expertise and knowledge to usefully contribute to the development and evaluation of these programs.

Youth Suicide Prevention

Youth Suicide Advisory Committee (YSAC)

SR Silburn, SR Zubrick,
JAM Cugley, A Green,
S Hillman, D Casey,
A Robson, A Gowing, N Kerr.

Sven Silburn and Stephen Zubrick provide research and administrative support to the State Government's inter-departmental and inter-sectoral advisory committee on suicide prevention. Jenny Cugley provides administrative support to the committee through the role of Executive Officer. This has enabled the Committee to carry out its day-to-day business and correspondence, including maintenance of records, preparation of responses to Ministerial, Parliamentary and other inquiries, preparation of an annual report to the Minister, dissemination of factual information, applications for project funding, and provision of research and statistical consultancy services.

Sharon Hillman maintains the Coroner's Database on Suicide. The Database provides data to identify needs, measure trends and advance knowledge about current risk factors. This has contributed to policy development in the area of public health and helped with the establishment and evaluation of clinical and community interventions. Sharon Hillman, Sven Silburn, Andria Green and Stephen Zubrick also investigated the contribution of cannabis and other drugs to the suicide of young people in Western Australia from 1986 to 1998, on behalf of the Western Australian Drug Abuse Strategy Office.

A report on the needs of people bereaved by suicide was produced by Sharon Hillman, Andria Green and

Sven Silburn. This has led to a proposal, funded through the National Suicide Prevention Strategy, to develop an information pack for those bereaved by suicide.

Sven Silburn has also been responsible for providing technical advice to the WA Auditor General's office which is currently conducting a performance review of the clinical management of deliberate self-harm admissions in Western Australian public hospitals. This review is examining the level of implementation of the State's Clinical Health Goals and Targets in this area and the extent to which current hospital practice accords with the clinical practice guidelines jointly published by the Australasian College of Emergency Medicine and Royal Australian and New Zealand College of Psychiatry in 2000.

Sven Silburn continues to provide support and consultation through the Aboriginal Youth Suicide Prevention Steering Committee for the implementation of strategies, by relevant Government agencies, addressing the recommendations of the *Across Government Policy and Programs for Preventing Suicide and Suicidal Behaviour Among Aboriginal Youth in Western Australia*, (November 1998). Anna Robson has been employed through funding from the Aboriginal Affairs Department to assist with development of the final recommendation, seeking to achieve good community consultation around promoting positive mental health, well-being and resiliency for all Aboriginal children, young people and their families.

Dan Casey has supported the Regional Trainer program to ensure the availability, for workers with young people, of Gatekeeper workshops statewide. The training promotes best practise guidelines and interagency consultation and collaboration to support both the worker and the person at risk. The Western Australia Schools' Strategy for suicide prevention is also monitored and supported. The Regional Training program was successfully introduced in Tasmania under contract with the University Department of Rural Health, Tasmania. Funding over a three year period has been secured, through the National Suicide Prevention Strategy, to develop a sustainability plan for the Regional Trainer program. Administrative support to the Regional Trainer program was provided by Anne Gowing and by Nikki Kerr in the latter part of the year.

Division of Population Sciences

Antecedants and Outcomes of Newborn Encephalopathy (NE) in Term Newborns

Cohort Studies

Newborn Encephalopathy (NE) Study

N Badawi (The Children's Hospital at Westmead, NSW), JJ Kurinczuk (University of Leicester, UK), PA Alessandri, GN Dixon, K Dixon, P Serna, FJ Stanley, S Silburn, SR Zubrick, JM Keogh (Hornsby Ku-Ring-Gai Hospital, NSW), PR Burton (University of Leicester, UK), J Valentine (Princess Margaret Hospital).

Newborn encephalopathy (NE) is an important clinical problem that has traditionally been associated with 'birth asphyxia'. To date, many studies have been premised on this causal assumption which has also been central in assigning blame in obstetric litigations. Of those conducted, the majority were not population based, most concentrated on encephalopathy while others only included infants with neonatal seizures. Few studies have been concerned with outcomes other than cerebral palsy and death. With notable exceptions other disabilities such as cognitive impairment and developmental delay have not been considered or have only been reported for infants with hypoxic ischaemic encephalopathy.

We undertook a case control study of moderate and severe newborn encephalopathy with recruitment from June 1993 to December 1996. This was the first population-based study of newborn encephalopathy using a broad clinical definition that investigated the possible associations between NE and a series of preconceptional, antepartum and intrapartum characteristics. Our analyses of these associations have led us to conclude that the causes of NE are heterogeneous and many of these were found to relate to the antepartum period.

We have subsequently followed the cases and controls longitudinally to ascertain developmental status of the children in their second year of life, and their later neurological, cognitive and behavioural outcomes. To date 14% of NE cases and one control child have died. Overall 10.1% of the cases have been notified to the WA Cerebral Palsy Register as having cerebral palsy. This figure is likely to increase as the population of children age and continue to be diagnosed and notified to the Register.

A Griffiths Mental Development Scales assessment was performed on 190 cases and 443 controls at a mean age of 16 months. Four cases and two control children received alternative developmental

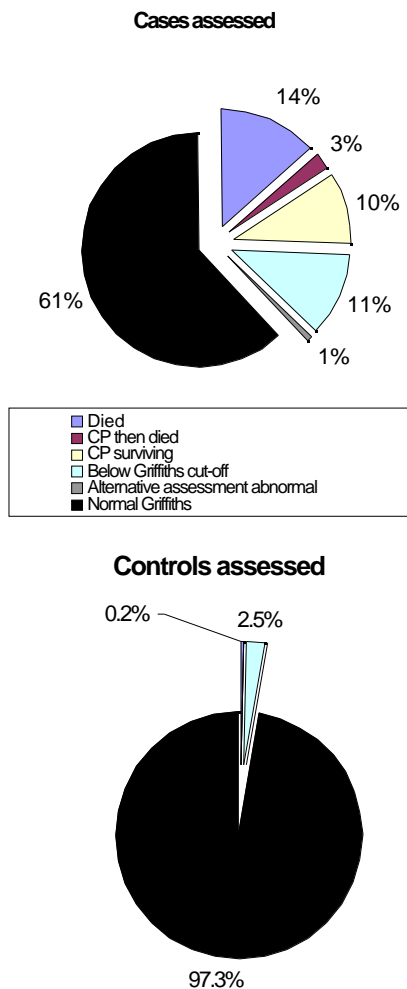


Figure 1. Early developmental outcomes for cases with a history of newborn encephalopathy (N=229) and controls (N=446)

assessments and one case was too disabled to be assessed with formal instruments. The developmental follow-up fraction was 81% of eligible cases and 79% of eligible controls.

The mean general quotient (GQ) for the controls were normally distributed. The population mean and standard deviation (sd) for the GQ score were calculated for the controls. A cut-off of two standard deviations below the control population mean GQ score was used to identify cases and controls with a clinically significant degree of developmental delay. The findings from our population based study indicate that NE places infants at significant risk of developmental delay by the second year of life. We found differences in all areas of development as assessed with the Griffiths Mental Development Scales that were both statistically and clinically significant. Of note the largest deficits were seen in speech and hearing which are crucial areas for all aspects of development and learning. Figure 1 summarises the early childhood outcomes for the cases and controls. 39% of the cases had a poor

outcome in early childhood as defined by death, cerebral palsy or significant developmental delay, compared to 2.7% of the controls. The 47 cases and 118 controls eligible for assessment who were not assessed are known to be alive and do not have cerebral palsy, however, their developmental status is not known. If we assume that all the unassessed cases and controls had a GQ score above the cut-off, then overall a third of cases would have a poor outcome compared to only 2.1% of the controls ($P < 0.001$).

When the children reach three years of age they receive a full neurological assessment performed by a paediatrician. Currently 63% of the cases and controls have undergone a neurological assessment and the follow-up continues to be arranged for those 'hard to contact', rural, interstate and overseas participants. Psychological assessment at age 5 years is underway with a follow-up fraction of 57% of eligible children to date. These assessments include receptive language, verbal and visual reasoning, verbal short-term memory and retrieval and application of knowledge. Parents also complete a questionnaire on their child's temperament, behaviour and current medications.

Comprehensive questionnaires on the demographics, social and psychological functioning of each family are being collected as the children turn six and then seven years. A further assessment is due to commence in mid 2001 when the oldest children in the study turn eight years. This assessment is designed to collect information on each child's current school performance as well as their level of behavioural, neurological and cognitive functioning.

Chief Investigators

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Francine Eades *DipAppSc(Nursing)*

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Sharon Hillman *BA(Psych) BPsych*

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Helen Howells *DipFashDes*

Paul Ishiguchi *DipHlthSci (ECowan)*

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Marnie Richardson *BA(Hons)*

Deborah Robertson *BA DipEd MPhil*

Sven Silburn *MSc (Clin Psych)*

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Casual Surveyors - 120 trained

Students

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External Committees

SR Silburn. Member, Ministry of Justice Suicide Prevention Taskforce Steering Committee.

SR Silburn. Member, Evaluation Committee MindMatters: National Mental Health in Schools Project.

SR Silburn. Member National Mental Health in Schools Project.

SR Silburn. Member of the WA Ministerial Youth Suicide Advisory Committee.

SR Silburn. Member, Research Subcommittee, Western Australian Health Promotion Foundation.

A Williams. Member of the National Working Party on Mental Health Prevention and Promotion, Commonwealth Department of Health and Aged Care.

A Williams, SR Silburn, SR Zubrick. Members, Interagency Committee on Children's Futures (Western Australian Senior Officer's Forum).

SR Zubrick. Chairperson, Management Committee Auseinet - the Australian Network for Promotion, Prevention and Early Intervention for Mental Health.

SR Zubrick. Member of the Child and Adolescent Mental Health Advisory Group, National Mental Health Survey, Mental Health Branch, Commonwealth Department of Health and Human Services.

SR Zubrick. Member of the WA Ministerial Youth Suicide Advisory Committee.

SR Zubrick. Member of the National Working Party on Mental Health Prevention and Promotion Commonwealth Department of Health and Aged Care.

Biostatistics And Genetic Epidemiology

Methodological Research in Biostatistics and Genetic Epidemiology

P Burton
(Leicester
University),
L Palmer (Harvard
Medical School),

K Scurrah (Leicester University), N Sheehan
(Leicester University)

The year 2000 has been most productive. Our work in genetic epidemiology has advanced on several fronts. (1) We published a major methodological paper [Scurrah et al, 2000] describing the application of generalised linear mixed models (GLMMs) fitted using Gibbs sampling (in WinBUGS), to traits reflected in a censored failure time (e.g. an age at onset) and to extended pedigrees. (2) We demonstrated the utility of these models in one of the most successful analyses of the simulated general population data at Genetic Analysis Workshop 12, in San Antonio, Texas [Scurrah et al, publication in press]. (3) We commenced work on the introduction of adjustment for non-random ascertainment to our models resulting in a stimulating piece of collaborative research with Professor Robert Elston's group in Cleveland, Ohio [Burton et al, 2000]. (4) We have recently commenced work on the incorporation of simultaneous linkage analysis in our models, and as a key precursor to this extension we have a paper in press describing the introduction of a segregation component to model the effect of an unknown major gene [Palmer, Cookson et al, publication in press]. (5) On the applied side we worked closely with Dr Lyle Palmer in his analysis of the COAG meta-analysis of chromosome 5q linkage studies for asthma related traits [Palmer, Barnes et al, publication in press], a meta-analysis originally set up by Professor Newton Morton. Indeed the pressing need to introduce ascertainment corrections to our models for this analysis was the initial spur for our work with ascertainment. Our more general work on the application of Bayesian methods to problems in medical science was also rewarded by the publication of an invited paper describing our methods based upon the uniform prior; an approach which we worked on during the first four years of the Program Grant [Gurrin et al, 2000]. Finally, new collaborative work with the medical statistics group in Leicester (Professor David Jones' group) has led to a recognition of the potential utility of the approach we call 'data inflation' (which we described in one of our genetic epidemiology papers in 1999), as a means of greatly reducing the sensitivity of Bayesian mixed models to the choice of vague priors for the between group variance component. This looks to have important applications in meta-analysis.

We were delighted to recruit Dr Nuala Sheehan in July 2000. She has continued pre-existing work on the development and investigation of models for very complex pedigrees, and the implementation of these models in a graphical modeling package (HUGIN). She had a major methodological paper published during 2000 which addresses many of the key issues pertaining to the use of Markov chain Monte Carlo methods (including Gibbs sampling) to problems involving complex pedigrees [Sheehan, 2000]. There are important parallels between the models (for Normal traits) that she has developed and our pre-existing work with GLMMs. We believe that these parallels will assist us in our, now joint, aim to introduce a linkage component to the GLMMs. At the same time, we believe that our pre-existing work with GLMMs and ascertainment will further Nuala's aims to implement her methods in HUGIN – work that is being carried out in collaboration with Dr Daniel Sorensen and Professor Steffen Lauritzen in Denmark. Nuala's next immediate objective is to commence work with causal models using methods described recently by Steffen Lauritzen with the aim of using these models to analyse the causal structure underlying newborn encephalopathy – a key aim of the NE study. This work will form a major part of the work to be undertaken by Nuala on her forthcoming visit to Western Australia. Both Paul and Nuala have been involved in a number of different workshops across Europe. The Workshop in Statistical Genetics held in Stockholm was particularly stimulating, and helped to strengthen pre-existing links between the Program Grant team and Professor Juni Palmgren who is based jointly at the University of Stockholm and the Karolinska Institute.

The Western Australian Twin Child Health Study (WATCH)

J Hansen,
P Alessandri,
N de Klerk,
M Croft, A James
(Sir Charles Gairdner Hospital), K Taylor (Curtin
University), P Burton, J Sleith, L Watts



The WATwin Register was established by the Western Australian Twin Child Health (WATCH) study in 1997 with funding from Healthway, and comprised data on all WA multiple births between 1980 and 1992 inclusive. The aim of this study was to investigate the roles that genes and the environment play in the development of asthma and allergies. Families were asked to complete three

lengthy questionnaires, one for the multiples, one for their parents, and one for any siblings they had. They covered a wide range of demographic, behavioural, health and medical questions, with the main concentration being on asthma and allergies. There were over 100 questions to answer for every member of the family, and estimates of time taken to complete ranged from 30 minutes to over 2 hours. After the study had been running for 8 months, we developed a much shorter questionnaire, as many families stated that they did not have the time to complete the longer versions. About 14% of families opted to complete this revised questionnaire. The percentage of families who returned completed questionnaires was about 60%, irrespective of whether the 'long' or 'short' questionnaires were used. Eighty eight percent of families indicated that they were happy for us to contact them in the future to be invited to take part in further studies. This percentage did not differ between 'long' or 'short' questionnaires, although families of multiples aged 10 years or younger were more likely to have responded positively to this request (92% vs 84%, $p < 0.001$).

There was no difference in response, to either the initial letter or to the questionnaires, between metropolitan and non-metropolitan residents. Mothers who were under 20 years old when their multiples were born, were less likely than older mothers to respond to the invitation to participate (46% vs 80%, $p < 0.001$), but once they had agreed to participate there was no difference in the proportion who returned completed questionnaires (82% vs 90%, $p = 0.174$).

Analysis of the questionnaire data shows that:

- 68% of families live in the Perth metropolitan area
- 54% of twins have older siblings
- 22% of fathers and 18% of mothers have tertiary education
- 86% of mothers and 85% of fathers are in their first marriage
- 98% of fathers and 66% of mothers work outside the home
- 64 fathers (2.3%) and 60 mothers (2.1%) are twins themselves
- 61% of fathers and 71% of mothers reported that they have not smoked regularly since the birth of their multiples

A number of outcomes in the twins show evidence of a genetic component, as assessed by greater concordance between MZ twins compared with DZ twins. These include doctor diagnosed asthma (DDA), had ever wheezed, had wheezed in the last 12 months, hay fever, eczema, and ADHD, both hyperactive and inattentive types.

Factors which appear to increase the risk of DDA are:

- having an asthmatic mother and asthmatic father
- being diagnosed with hay fever or eczema
- being born under 33 weeks' gestation

Having older siblings seems to decrease the risk of DDA.

Factors which appear to increase the risk of ADHD (hyperactive type) include:

- mother reports to have smoked during pregnancy
- having ever wheezed
- male sex and
- father being unemployed

WATCH Asthma and Atopy Study

A grant from NHMRC has allowed us to extend the

Register to include WA multiple births in 1993 and 1994. A further 698 multiple birth families have been identified. Eighty five percent (561) of eligible families have been contacted and completed questionnaires have already been received from 337 (60%) of them. Follow-up of non-responders is continuing and the 1995 data will be included when they become available. The questionnaire developed for these families is much shorter than previous versions and only contains questions on family structure, pre- and post-natal factors such as periconceptual multivitamin use, smoking and breastfeeding, and several questions about asthma, including diagnosis by a doctor (DDA). The main function of this questionnaire is to enrol the family on the WATwin Register, and to ascertain concordance of DDA in twins. Planning is now underway for the next phase of the WATCH study, that is, phenotyping for asthma and allergies. Families, consisting of the twins, their biological parents and any of their siblings aged 7 and over,

will be invited to attend one of our clinics to undergo a series of standard breathing, allergy and blood tests. We will also be offering a free zygosity test to families who are unsure of the zygosity of their twins. Our plan is to recruit 60 multiple birth families from each of 6 birth years (1990 to 1995 inclusive), a total of 360 families.

WATCH Language Development Study

Participants

The sampling frame for this study consisted of all multiples born in Western Australia (WA) between September 1997 and August 1998 and 424 singletons in the same birth cohort as the multiples who were selected at random from the Midwife's Notification of Birth Records. The aim of the prospective part of WATCH was to investigate early language development and temperament in young twins and singletons and to recruit multiple birth families to the WATwin Register.

Multiples

Mothers of multiples were identified using the Midwife's Notification System. There were 362 twin pairs and 12 sets of higher order multiples (i.e., triplets, quadruplets or quintuplets) born during this period ($n = 374$). The names of all multiples were checked against WA mortality data provided to the TVW Telethon Institute for Child Health Research by the Registrar General's office on a monthly basis. Nineteen families experienced the death of one or more of their multiples and were not contacted as part of this study. The names of mothers were sought on the WA electoral roll held at the Department of Public Health at the University of Western Australia to ascertain a postal address. Addresses that were not traced via the electoral roll were then sought in the Telecom White Pages. Of the 355 eligible families, 352 (99%) were traced to a postal address and were sent an information sheet about the study and an expression of interest approximately one month prior to the multiples' first birthday.

Two hundred and sixty one (74%) families returned expressions of interest and agreed to participate; 25 (7%) families indicated that they did not want to participate; 55 (16%) families did not respond; and 11 (3%) of the letters were returned to sender. Questionnaires were sent to 261 families who agreed to participate just prior to the multiples' first

birthday. The parents were asked to return the questionnaires within a month. Two hundred and twelve (81%) families returned year 1 questionnaires; 47 (18%) families did not respond and one family withdrew from the study. The 212 families who returned year 1 questionnaires, plus one family who did not complete the Year 1 questionnaire were sent year 2 questionnaires just prior to their multiples' second birthday. The parents were again asked to return the questionnaires within a month. At the two-year-old follow-up, 145 (68%) questionnaires were returned; 62 (29%) families did not respond; 5 (2%) questionnaires were returned to sender; and 1 family withdrew from the study. Of the 261 participants, 144 (56%) families completed one-year-old and two-year-old questionnaires.

Singletons

Four hundred and twenty four families with singletons in the same birth cohort as the multiples were selected at random from the Midwife's Notification of Birth Records. Four hundred and five mothers were traced and contacted following the procedures described earlier. Two hundred and forty two families (60%) agreed to participate; 57 (14%) families indicated they did not want to participate and 105 (26%) families did not respond to the expression of interest. The same procedures for sending questionnaires described earlier were followed. Of the 242 families who agreed to participate, 204 (84%) returned year 1 questionnaires, 35 (14%) families did not return questionnaires and 3 (1%) families withdrew from the study. At the two-year-old follow-up, 153 (75%) questionnaires were returned; 47 (23%) families did not respond; 3 (1%) questionnaires were returned to sender; and 1 family withdrew from the study. Of the 242 participants, 153 (63%) families completed one-year-old and two-year-old questionnaires.

Results

These results are for 110/152 singletons and 212/278 twins for whom we have complete data at one- and two-years of age.

Language Development

Significantly more two-year-old twins (18.4%) than singletons (9.1%), $\chi^2 = (1, n = 322) = 4.86, p < .05$ presented with expressive vocabulary scores at or below the 5th percentile on the MacArthur Communicative Development Inventory: Words and Sentences instrument. This equates to a productive vocabulary of less than 48 words in boys and 70 words in girls. There were no sex differences in late talker status at two years of age for twins or

singletons. The 5th percentile criterion for language delay is similar to the 50 words or less expressive vocabulary criteria adopted by other researchers. The finding that 9% of singletons scored below this cut-off is strikingly similar to the prevalence estimates of late talking in other research involving singletons. This finding that twice as many twins compared to singletons were late talkers at two concurs with previous research involving twins.

Temperament

When the temperament characteristics of twins and singletons were compared, the only difference was that twins were more rhythmical than singletons (i.e., their routines were more regular). Twins and singletons did not differ in approach/withdrawal; cooperation/manageability; distractibility; persistence, or reactivity. Subsequent analyses with the complete data-set will (1) investigate characteristics of language development at 12 months that predict language development (i.e., normal or delayed) at 24 months for twins and singletons and (2) compare temperament characteristics in twins and singletons with normal and delayed language development.

Benefits

Language impairment in children is a classic example of a complex, multifactorial disorder of human communication, with poorly understood interrelationships among factors that influence variability and susceptibility to disease and response to treatment. While the developmental outcomes for late talkers in the prospective part of WATCH are currently unknown, through WATCH we have identified a unique population-based birth cohort of late talking multiples and singletons who can potentially be recruited to further studies in language development and disorders in WA children.

Biostatistical Analysis and Support

N de Klerk, J Hansen, H Teasdale, M Firth

This group continued collaborative work with other project throughout the Institute and with the Departments of Paediatrics and Public Health, in particular in areas involving the analysis of complex longitudinal data and survival analysis.

Breast Feeding and Atopy

W Oddy, J Sherriff (Curtin University), J Peat (Institute of Respiratory Medicine, Sydney), N de Klerk.

Wendy Oddy commenced her post-doctoral fellowship at Curtin University. This involves continued collaboration with the Institute in the analysis of data from various studies. The work at Curtin has included being course coordinator in the Degree of Masters of International Health, Centre for International Health; responsibility for the 'Evaluation and Research in Health' unit, and the 'Maternal and Child Nutrition' modules in the 'Maternal and Child Health in Developing Countries' unit; Development of the International Nutrition 600 postgraduate distance education unit; development and delivery of lectures in the Nutritional Epidemiology 382 Unit to third year nutrition students; supervision of two third year nutrition student research projects. The fellowship also involves collaboration with Institute of Respiratory Medicine in Sydney where Wendy made several presentations during October.

Staff and Students

Biostatistics and Genetic Epidemiology

Head

Nicholas de Klerk *BSc MSc PhD*

Staff

Phyllis Alessandri

Marty Firth *BSc(Hons)* from December

Janice Hansen *BSc(Hons) MPH*

Lyle Palmer *BSc(Hons) PhD*

Gail Reading *BSc(CompSci)*

Jan Sleith

Lin Strauss

Helen Teasdale *BSc(Hons)* until September

Lynn Watts

Students

Kate Brameld *BSc(Hons) PhD* candidate

Maxine Croft *BAppSci* PhD candidate

Janice Hansen *BSc(Hons) MPH* PhD candidate

Jacqui Joseph-Bowen *BScOT*

PGradDip(HlthAdmin) MSc(Addiction) PhD candidate

Honorary Research Fellow

Wendy Oddy *BAppSci MPH*

Awards

LJ Palmer. Churchill Fellowship, Winston Churchill Memorial Trust, 1999-2000.

LJ Palmer. Fulbright Fellowship, Australian-American Educational Foundation, 1999 - 2000.

W Oddy. NHMRC Public Health Postdoctoral Fellowship, Curtin University, 2000-2004.

Theses passed

W Oddy. Breast-feeding and the development of asthma and atopic disease in children. PhD, Department of Paediatrics, The University of Western Australia.

V Williams. Measures of pulmonary fibre burden in Western Australia: Association with exposure to asbestos and occurrence of asbestos related disease. PhD, Department of Public Health and Department of Pathology, The University of Western Australia.

Invited Presentations

N de Klerk. Lung cancer caused by industrial exposure. World Congress on Lung Health, Florence.

N de Klerk. Dietary associations in high risk subjects exposed to asbestos. Western Australian Inaugural State Cancer Conference, Perth.

N de Klerk. Air quality, mortality and hospital morbidity in Perth, Western Australia, 1992-1997. International Clean Air and Environment Conference, Sydney.

W Oddy. Omega-3 fatty acids and childhood asthma: a nested case-control study. Nutrition Society of Australia Scientific Meeting, Fremantle.

W Oddy. Asthma prevention: the role of infant feeding. Australian Lactation Consultants Association National Conference, Melbourne.

W Oddy. Early introduction of other milk increases the risk of hospitalisation due to respiratory disease in infants. Australian Lactation Consultants Association National Conference, Melbourne.

External Committees

NH de Klerk. Australian Radiation Health and Safety Advisory Council.

NH de Klerk. Clinical Drug Trial Committee, Sir Charles Gairdner Hospital.

NH de Klerk. Mesothelioma Committee of Western Australia.

NH de Klerk. Scientific Advisor, Panel on: European Communities - Measures Affecting Asbestos and Asbestos Products, World Trade Organisation, Geneva.

NH de Klerk. Western Australian Air Quality Co-ordinating Committee Health Issues Group.

W Oddy. International Society for Research into Human Milk and Lactation, Elected Member, 2001.

W Oddy. Public Health Association of Australia Executive Child Health Special Interest Group - Invited position, Nov 2000.

W Oddy. National Food and Nutrition Monitoring Project, Breastfeeding Reference Group (Australia).

W Oddy. Breastfeeding Public Health Action Group, Health Department of Western Australia

W Oddy. Nutrition Advocacy Group, with Cancer Foundation of WA, Perth, Western Australia.

LJ Palmer. Greater Cleveland Asthma Coalition, Cleveland, Ohio, USA.

LJ Palmer. Joint Principal Analyst (with Professor Newton Morton), International Consortium on Asthma Genetics (COAG).

LJ Palmer, NH de Klerk. Busselton Population Research Foundation Board of Directors.

LJ Palmer, NH de Klerk. Perth Respiratory Epidemiology Group (PREG) Executive Committee.

LJ Palmer, NH de Klerk. Scientific Advisory Committee of the Busselton Research Foundation Board.

Aboriginal Health Research

Bibbulung Gnarneep ("Solid Kid")

SJ Eades, AW Read,
L Alessandri
(deceased), J Nannup,

J Johnston, A Mahony, S Peel, N Pavy-Bell, K Jones,
T Eades

Bibbulung Gnarneep



The Bibbulung Gnarneep project comprises a program of collaborative research with the Aboriginal community of Perth and environs. Initially, the project focussed on a prospective cohort study following children from six to twelve weeks old up to the age of two years. In a series of five interviews with mothers, information was collected on a wide range of

variables impacting on the health of the children. Particular attention was given to elucidating the difficulties and barriers that mothers faced in rearing healthy children (solid kids). Information regarding the children's illnesses has been collected from the mothers and also from health care providers.

Analysis of these data is providing valuable information to produce health promotion materials and to devise evidence based policies with the aim of improving the health of Aboriginal families. The most recent analyses have focussed on nutritional aspects of the study including breastfeeding. It was found that more than half the babies (51%) were still receiving some breast milk at ages seven to eight months, with 54% being exclusively breast fed for at least three months. Brochures with appropriate information on children's nutrition are now being developed with the community.

Another response to the results has been the implementation of a pilot home visiting program for pregnant Aboriginal women, and 15 women enrolled in the last few months of 2000. The main aim of the program is to provide support and advocacy for the women, not to replace their usual antenatal or other care. Evaluation of the program will include quantitative and qualitative outcomes including acceptance of the various components by the women involved. We are fortunate in having an Aboriginal midwife and a health worker to conduct the project and provide the home visits, and the study is already providing valuable information on which to base a model home visiting program for Aboriginal women residing in a major metropolitan area.

Kulunga Research Network

D McAullay,
SJ Eades, AW Read
and J Johnston



The network is a joint initiative between the Western Australian Aboriginal Community Controlled Health Organisations (WAACCHO), the Derbarl Yerrigan Health Service and the Institute, and was established in the second half of 1999.

Young Aboriginal mother Marika Eades and her three children, Duana and twins Levi and Kelston officially launched the Kulunga Research Network on 31 August. Network Patron, Dr Lowitja O'Donoghue was unable to make it to the launch but sent a special video message of congratulations to the team, applauding their research efforts in Aboriginal health. Patron in Chief of the Network, His Excellency The Honourable Sir William Deane AC KBE, Governor General of the Commonwealth of Australia, was also unable to attend the launch, but met with members of the Aboriginal research teams on Friday 1 September.

The primary philosophy of the Network is to act as an advocate for Indigenous children and families in Western Australia. The principal aim is to ensure that community based and culturally relevant research benefits families by influencing policy and planning in government and other key agencies. Another major objective is to enable Aboriginal and Torres Strait Islander people to be involved in all areas of research and implementation of outcomes. We believe that this philosophy is the key to success in realising improved Indigenous health. The network will implement this philosophy by focusing on Indigenous projects in close collaboration with Aboriginal Medical Services and other community-controlled health organisations.

The Network encompasses all of the Aboriginal health projects conducted by the Institute and collaborative partners. These projects include Bibbulung Gnarneep ("Solid Kid"), the Western Australian Aboriginal Child Health Survey, the

Kalgoorlie Otitis Media Study and the Swimming Pool Study.

Several projects are currently in the planning stage and will commence in 2001. These include a community dental health perception project, the use of Aboriginal Health Worker antenatal and early postnatal education packages and a youth health needs analysis project. As the Institute has been very successful in carrying out research with genuine Indigenous relationships, the Network has set aside the year 2001 to focus on building the community's capacity to carry out their own research. This will involve the key areas of training and information.

Risk factors for otitis media in Indigenous and non-Indigenous children in the Kalgoorlie-Boulder area

D Lehmann,
D Elsbury,
R Monck,
K Sivwright in
collaboration with
L Dorizzi (Bega

Garnbirringu Health Services Aboriginal Corporation), J Tamwoy and P McIntosh (Ngunytju Tjitji Pirmi Inc), HLC Coates (Senior ENT Surgeon, Princess Margaret Hospital), TV Riley (Department of Microbiology, The University of Western Australia), K Meiklejohn (Regional Audiologist, Northern Goldfields Health Service), S Weeks (Audiologist, Disability Services Commission), AW Cripps (Faculty of Applied Science, University of Canberra), J Bowman (Pathcentre), J Spencer (The University of WA Rural Paediatric Unit)

Enrollment into a study aimed at identifying the most potent factors predisposing Indigenous and non-Indigenous children to otitis media began in April 1999. Funding has been provided by Healthway. Babies are being followed closely from birth to age two years with specimens collected and clinical follow-up done on 7 occasions. Mucosal immune status is being investigated by collection of saliva and breast milk samples. Data on demographic, socioeconomic, environmental risk factors are also being collected. Nasopharyngeal aspirates are collected to investigate upper respiratory tract bacterial carriage. Ear health is assessed three times by an ENT specialist and hearing assessed once in the second year of life. We have now enrolled 130 children, 50 of whom are Indigenous. *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* have all been isolated from participants aged less than 6 months. We will continue recruiting babies for a further 18 months while carrying out detailed laboratory investigations and commencing data analysis.

Findings from this study will be used to develop appropriate interventions to prevent otitis media, which can seriously affect childhood development, school performance and subsequent social and economic well-being.

Socioeconomic risk factors and treatment-seeking behaviour for otitis media in the Aboriginal population of Kalgoorlie-Boulder region

D Lehmann,
D Elsbury,
J Johnston,
A Mason,
Dr C Jeffries-Stokes (UWA Rural Paediatric Unit)

As part of an NHMRC Otitis Media strategic research initiative, we were awarded a grant to investigate perceptions of ear disease in young children and treatment-seeking behaviour for otitis media in the Indigenous population resident in the Kalgoorlie-Boulder area and to identify socio-economic barriers to compliance with recommended treatment for otitis media.

We have been collecting qualitative data which are essential to supplement the quantitative data being collected in the larger cohort study described above in order to develop appropriate intervention programs for prevention of otitis media and its serious consequences, in particular hearing loss. Through community workshops and individual interviews we have been collecting information on people's perceptions and concerns about middle ear infections, when and why they seek treatment, and any difficulties they may encounter in receiving and completing prescribed treatment. A total of 70 interviews have been completed, results have been entered on computer file and analysis will begin shortly. At the same time, data are being collected in the above-mentioned cohort study to investigate socioeconomic, nutritional and environmental factors, which may predispose babies to otitis media.

Impact on health of children and adolescents of introduction of swimming pools into remote Aboriginal communities

D Lehmann,
M Tennant,
D Silva,
D McAullay,
K Syvwright,
I Nannup,
F Stanley, A Read,

in collaboration with HLC Coates and F Lannigan (ENT Surgeons, Princess Margaret Hospital), B Currie and KS Sriprakash (Menziess School of Health Research, Casuarina, Northern Territory)

As part of an environmental intervention, the Ministry of Housing has built swimming pools in three remote Aboriginal communities in Western Australia. These pools at Burringurrah, Jigalong and Yandeyarra were officially opened by The Honorable Kim Hames (State Minister for Housing, Aboriginal Affairs and Water) in September 2000. The Institute for Child Health Research has been asked by the Minister to evaluate the impact swimming pools may have on health of children and adolescents in selected communities. This is being done by medical examination before and one year after the pools have been opened in Burringurrah and Jigalong. Children are being assessed to see whether there are any changes in the burden and severity of ear, eye, and skin disease as well as their general well being.

After preliminary visits to plan the study with the local communities, investigators visited the communities in July and August 2000 and collected demographic information, information about where and how often children swim, school attendance, and parents' views on the pools. In each community 60 children were enrolled into the study. These children were examined by a paediatrician. Ear health was assessed by clinical examination, tympanometry and a hearing test; pictures of the ear drum have been taken with a video-otoscope and stored on computer file. Those children with severe ear disease were examined by an ENT specialist, who also reviewed the stored photos of eardrums. Swabs of some skin sores were taken in order to provide information on the strains of Group A *Streptococcus* circulating in communities and to determine whether there is any

change in strain distribution after children have swum in the pool. From the local clinic records, we are collecting information on all episodes of disease (including prescriptions of antibiotics) for one year prior to opening of the pools and for the entire year of follow-up. In an attempt to have some measure self-esteem, children were asked to draw pictures of themselves in the pool and this will be repeated in a year's time. Informal community discussions were held to determine expectations, concerns and social changes that may occur as a result of the pool.

A mid-summer visit to assess ongoing morbidity and identify any epidemics that may have occurred since the opening of the pools will be done in March 2001. Researchers will return later in 2001 to look for any changes in the prevalence and severity of otitis



media, ear drum perforation, ear discharge, hearing loss, nasal discharge and loose cough as well as skin infections.

Studies in Cerebral Palsy

Studies in Cerebral Palsy

F Stanley, E Blair,
L Watson, J de Groot,
J Smith, B Petterson,

J Slee, N Badawi

The changing epidemiology of cerebral palsy (CP)

The WA Cerebral Palsy Register continues to monitor the occurrence of cerebral palsy overall and in relevant subgroups such as low birth weight, preterm and multiple births, type and severity, and presence of other disabling conditions. Updating of data was complete to the 1994-born cohort in December 1999 when the *Report of the Western Australian Cerebral Palsy Register* was published. Updating of data for the 1995- and 1996-born cohorts is now in progress and nearing completion.

While the original aims of the Cerebral Palsy Register focused on aetiological studies, our data are of considerable relevance to the problems of living with cerebral palsy. In recognition of this we have invited two parents of persons with cerebral palsy (one a child and one a young adult) to join the Advisory Committee. During 2000 Cerebral Palsy Studies hosted a 'Cerebral Palsy Think Tank' at the Institute to which all persons with an interest in any aspect of cerebral palsy research were invited with a view to combining our research capabilities to best further knowledge about cerebral palsy. This movement falls naturally into two overlapping interest groups, *Aetiology* and *Living with cerebral palsy*, both of which involve Cerebral Palsy Studies staff.

Living with cerebral palsy

Classifying overall disability (resulting from all impairments) is relevant to the assessment of long term outcome and to planning service requirements of persons with motor impairment (cerebral palsy). With staff of the Cerebral Palsy Association, a classification of overall disability was devised. There was a peak in overall disability among children with cerebral palsy in the 1988-92 birth cohorts. Although this has been self limiting, this cohort will have a significant impact on service requirements in the coming decades as they grow up. Our study of survival shows that overall disability correlates well with life expectancy. These survival data are unique in Australia, are frequently requested and their publication is keenly awaited by families, service planners and the legal profession alike. Studies carried out in collaboration with the Department of Paediatric Rehabilitation at Princess Margaret Hospital and the Physiotherapy Department at Curtin University on the use of botulinum toxin in

the management of hemiplegic and of diplegic cerebral palsy are now complete. Further studies of the use of botulinum toxin in much younger children are being planned.

Aetiology of cerebral palsy

Data collection for the large case-control study of cerebral palsy and perinatal mortality in term and preterm births born 1980-1994 is progressing. Many rural hospitals and general practitioners were visited in 2000 and collection of hospital data pertaining to cases of cerebral palsy and controls is scheduled to be completed in 2001. Aetiological studies pursued during 2000, in part preparatory to the analysis of the case-control data, include

examining the relation between risk of cerebral palsy and mode of delivery in term infants

examining the relation between risk of death, cerebral palsy and/or cognitive disability and intrauterine growth in twins

examining the changing gestational age profile of very preterm born infants with cerebral palsy

reviewing the evidence for a relationship between infection of the placental membranes and cerebral white matter disease in infants born very preterm

During 2000 the Birth Defects Register was linked with the Cerebral Palsy Register to validate the information concerning birth defects in persons with cerebral palsy. The quality of these data were thereby improved in both collections. These data form the basis of a study of the aetiological significance of birth defects to cerebral palsy now in progress.

Members of the WA Cerebral Palsy Register Advisory Committee:

Dr Peter Chauvel, Developmental Paediatrician, Princess Margaret Hospital

Dr Noel French, Neonatal Paediatrician, King Edward Memorial Hospital for Women

Dr Rex Henderson, Director, Rural Paediatric Service

Dr Athel Hockey, Medical Geneticist, King Edward Memorial Hospital for Women

Dr Philip Montgomery, Medical Director, Disability Services Commission

Dr Lakshmi Nagarajan, Paediatric Neurologist,
Princess Margaret Hospital

Mrs Kerry Naso, parent representative

Dr Trevor Parry, Director, State Child Development
Centre

Dr Jon Silberstein, Paediatric Neurologist, Princess
Margaret Hospital

Dr Peter Silberstein, Paediatric Neurologist

Mrs Margaret Tait, parent representative

Dr Peter Walsh, Paediatric Neurologist, Princess
Margaret Hospital

Dr Jane Valentine, Developmental Paediatrician,
Princess Margaret Hospital

Dr Ian Walpole, Medical Geneticist, Princess
Margaret Hospital

Studies in Birth Defects

Studies in birth defects

C Bower, J Payne, P Serna,
J Kurinczuk, S Kwon,
L Colvin, M Hansen,

M Miller, in collaboration with Andrea Begley
(Curtin University), S Webb (Health Department of
WA)

Data collection for the *case-control study of birth defects* concluded in late 2000, and data entry is almost completed for the information collected from mothers of infants with birth defects and mothers of infants without birth defects. The participation proportion was 80%. The aims of the study are to evaluate the promotion of folate for the prevention of neural tube defects, and to investigate the role of folate in relation to other birth defects. Data analysis will be conducted in 2001.

A study of *births to non-Caucasian, non-Aboriginal mothers*, using linkage to the Maternal and Child Health Research Data Base, found that the 4.2% of all births 1985-1995 in Western Australia were to these mothers. Records of these mothers were compared with those of a 10% random sample of births to Caucasian mothers over the same period. Non-Caucasian mothers born in Vietnam and the Philippines had a 30% reduction in risk of having a baby with birth defects when compared to infants of Caucasian mothers. Non-Caucasian mothers born in India and Singapore had a slightly but not significantly reduced risk, and those born in Malaysia and New Zealand had a similar risk to Caucasian mothers.

An analysis of *hospitalisations in children with birth defects* in WA. Three year-of-birth cohorts (1980, 1985, 1990) were examined, and the hospitalisation experience of all children with birth defects in these cohorts were compared with all other children in the cohorts, using data on the Maternal and Child Health

Research Data Base. The Data Base has not been used extensively to analyse morbidity records on a total population basis and, thus, validating the linked data extracted for this project was an important aspect of the project. The data were analysed in 14 clinically relevant categories, three specific diagnostic or admission categories (asthma, tonsils, otitis media), eight major birth defect categories and some specific birth defect categories (hypospadias, talipes). A total of 70,237 children's records and 100,219 hospital admission records formed the database for the study. Up to the age of five years, 83% of all children with a birth defect had been admitted to hospital compared with only 46% of the children in the control group.

The study of *birth defects in infants born after assisted conception* was completed in 2000. The study included children conceived by intracytoplasmic sperm injection (ICSI), and by standard IVF and a comparison group of a random sample of naturally conceived infants delivered in Western Australia during the same time period (1993 to 1997). The design of this study has addressed the major methodological problems that have plagued previous researchers in this area. Birth defects were found to be about twice as common in infants born after assisted conception techniques, compared with naturally conceived infants, and the increase in risk remained after adjustment for maternal age, parity, sex of the infant, correlations within sibships, and when the analysis was restricted to term singleton infants.

Western Australian Birth Defects Registry Twentieth Anniversary Scientific Symposium

This Symposium was held at the Institute on Thursday 27 and Friday 28 April 2000, to celebrate the first 20 years of the Birth Defects Registry in WA. It was open to clinicians and researchers interested in birth defects within Australia and overseas, and to community groups providing support to the families of children with birth defects. There were 90 registrants for the Symposium, and over 160 attendees at the opening session.

Whilst the Registry is located at King Edward Memorial Hospital, it has always had strong links with the Institute. It was established by Professor Stanley in 1980, Dr Bower has been Medical Officer to the Registry since its inception, many of the studies conducted by Institute researchers use data from the Registry, and Registry data form an important part of the Maternal and Child Health Research Data Base.

In her welcoming address, Dr Bower paid special tribute to the many people and institutions providing support to the Registry over its first 20 years. Certificates of Appreciation were presented to Ms Rosemary Johnston, Mrs Robin Forbes, Ms Edwina Rudy and Mrs Aandra Ryan, in recognition and appreciation of their dedication and contribution to the work of the Registry.

There was a lively session on birth defects and assisted reproduction, with presentations from Dr Gillian Turner, a geneticist from the Hunter Health region in New South Wales, Dr Jack Goldblatt, Director of Genetic Services in WA, Dr Jennifer Kurinczuk, senior lecturer in reproductive epidemiology, at the University of Leicester, and Michèle Hansen, a Master of Public Health Student.

A further two sessions were devoted to neural tube defects, a particular research interest of the WA Birth Defects Registry. An Australasian overview of folate promotion and trends in neural tube defects was provided by Ms Maureen Bourne from the ACT, Dr Jane Halliday from Victoria, Dr Annabelle Chan from South Australia, Dr Barry Borman from New Zealand, and Ms Andrea Begley and Ms Margaret Miller from WA. Internationally, Dr Godfrey Oakley from Atlanta, and Dr Martha Werler from Boston, gave a United States perspective, and Dr RJ Berry reported on the large and recently completed cohort study in China.

The other keynote speakers were Professor Fiona Stanley, who discussed pathways to prevention of birth defects, and Dr Marsha Lynn Yeargin-Allsopp, an epidemiologist from Atlanta, who spoke about surveillance of developmental disabilities in the USA.

In addition, there were two sessions of proffered papers, a poster session, and displays provided by the Downs Syndrome Association, Heart Kids, the Hereditary Disease Unit, the Kalparrin Centre, the Rett Syndrome Association and the Spina Bifida Association.

The Symposium was generously supported by the Australian Birth Defects Society; Curtin University; Department of Public Health, The University of Western Australia; Hereditary Disease Unit – Health Department of WA; Human Genetic Society (WA Branch); King Edward Memorial and Princess Margaret Hospitals; Perinatal Society of Australia and New Zealand (WA Branch); Public Health Association (WA Branch); State Child Development Centre; The Friends of the Institute; and the TVW Telethon Institute for Child Health Research.

Studies in Intellectual Disability

Record Linkage

H Leonard, C Bower, B Petterson in collaboration with R Sanders (Education Department of WA)

The validation process on the Disability Services Commission (DSC) database undertaken in 1999 was continued during 2000 and included children more recently registered with DSC. Subsequent investigation of aetiological factors using the Maternal and Child Health Research Database (MCHRDB) are limited to children born in Western Australia (WA) and therefore we have confined our validation work to this group.

Not all children referred to DSC and entered on the DSC database will have an intellectual disability. The main purpose of our work has been to identify those children born in WA who do have an intellectual disability and thus remove the false positives from this dataset. At the same time, we have been attempting to identify children from other sources who have an intellectual disability but are not registered with DSC. During 2000, we were able to link the Special Education database from the Education Department of Western Australia to the MCHRDB and the DSC database. Preliminary results from these combined data sources show that

in children born in WA between 1983 and 1992, the prevalence of intellectual disability was 13.4/1000 live births. This was much higher than if restricted to children identified only through DSC. Nearly two thirds (62.9%) were male and 12.1% indigenous. Work for 2001 includes extending this analysis, where possible, to incorporate children from the independent and Catholic school systems.

There are many challenges to this work. Criteria for eligibility for different sources may be different. We have also shown that the level of handicap may not be reliable in those children where no IQ assessment is available. Nevertheless, national data now available show that neurodevelopmental disorders account for a sizeable proportion of children for whom a child disability allowance is claimed. Such data confirm the importance of identifying true trends and aetiological determinants of these disorders in our society.

Rett Syndrome

H Leonard, C Bower, S Leonard, T Schiavello, S Fyfe in collaboration with J Christodoulou, C Ellaway,

L Raffaele, B Bennetts, S Williamson (New Childrens Hospital, Sydney), M Davis (Royal Perth Hospital), M Msall, M Tremont

Ongoing national ascertainment of Rett syndrome continues. During 2000 cases were recruited through the Australian Paediatric Surveillance Unit as well as through the parent association (the Rett Syndrome Association of Australia). The former provides the opportunity for all clinicians who encounter a newly diagnosed case of Rett syndrome to notify the study. On registration of a new case both parents and clinician complete a questionnaire.

The need for information about the natural history of the condition is frequently highlighted by parents, physicians and therapists. The discovery of a genetic marker for Rett syndrome and hence earlier diagnosis further stresses the need for this kind of information. During 2000 with funding from the Financial Markets Foundation for Children our major project has been a follow up study which collects longitudinal data on children in our register. Throughout the year we conducted a calendar study. Parents recorded information on a daily basis in relation to episodes of ill health, medical, therapy and health appointments, hospital stays, nursing care and seizures. Medications were also charted. In the latter part of the year, using a comprehensive questionnaire, we collected data on behavioural features, educational and accommodation options

and the effects of Rett syndrome on the family. The questionnaire also included a version of the WeeFIM, a tool for measuring functional ability, and an instrument to collect data on handedness using questions designed by colleagues at University of California, Berkeley. In addition, the Rett Syndrome Symptom Index developed by Dr Ellaway was also included as was a modification of the Child Behaviour Checklist adapted for Rett Syndrome by Rebecca Mount at the Institute for Child Health Research in London. Analysis of these data will provide information on how Rett syndrome affects the child and the family on a daily basis. They will allow us to make international comparisons as well as to measure changes over time.

Parents were able to complete the Follow up Questionnaire on a paper copy or on an online version. This innovative technique allows automatic entry of data and reduces administrative costs. The Follow up Study will continue in 2001 with the completion of a further questionnaire, which will include measures of parental health.

The Molecular Genetic Studies continue in collaboration with the Sydney group. DNA collection continues throughout the country. Mutation screening has been completed on over 100 cases and on those cases mutations have been detected in 81%. Using the data collected from the epidemiological arm of the study we have conducted genotype-phenotype analysis and the first Australian publication is currently in preparation.

The year ended with the launch of the film "Silent Angels – A Rett Syndrome Story" which was held at the Institute. Over 160 people including families, friends, researchers, health professionals and teachers attended the screening. This was followed by a panel discussion on many aspects of Rett syndrome. The function was attended by Brett Aitken, an Olympic gold medallist whose daughter has the syndrome.

Throughout the year we have established and consolidated our international collaborative links. A paper relating to Preserved Speech in Rett syndrome is being prepared with a Rett syndrome study group in Japan. Further exploration of the Male Phenotype has been carried out in conjunction with Dr Carolyn Schanen at University of California. These and other international connections are the basis for our work in designing an international clinical database, which, with the international mutation database, will be the key to genotype-phenotype analysis.

The Western Australian Newborn Hearing Screening Programme

H Bailey, C Bower,
K Gifkins, J MacLean,
F Smith, J Zach,
R Clack, M Biggs,
R Jagnathan,

A McHarrie, M Gualda-Barr, L Hollywood, S Yong, L Hooper, A Freemantle, in collaboration with H Coates, J Krishnaswamy, N French, (King Edward Memorial Hospital and Princess Margaret Hospital for Children), C Bull, P Howes, (Australian Hearing Services); M Bulsala, Department of Public Health, The University of Western Australia, P Higginbotham, The Speech and Hearing Centre; J Richards, WA Institute for Deaf Education; S Weeks Disability Services Commission; V Verma, State Child Development Centre.

The Western Australian Newborn Hearing Screening Programme is jointly funded by the Health Department of Western Australia, King Edward Memorial Hospital for Women and Princess Margaret Hospital for Children and it is affiliated with the TVW Telethon Institute for Child Health Research. The aim of the programme is the early detection of hearing loss in babies in order to commence intervention by the time the baby with a hearing loss is six months of age. Speech and language development in children with severe to profound hearing loss is better if intervention is commenced before six months than if started later.

Newborn hearing screening involves a set of simple screens that are done prior to a baby's discharge from the maternity hospital. In 2000 the programme commenced at the five largest maternity hospitals in the Perth metropolitan area. Hearing screening is offered to all well babies on the second day of life. Babies who are admitted to a special care nursery are screened when at least 34 weeks gestation. If a good response is not obtained from the screening tests, the babies are re-tested in about two weeks. If there are not good responses in both ears at that stage, the baby is referred for diagnostic evaluation by a paediatric audiologist.

In 2000, nearly 7,500 babies received hearing screening. Over 99% of babies passed either the initial or repeat hearing screen. Two babies who were referred to a paediatric audiologist were subsequently diagnosed as having severe to profound bilateral sensori-neural hearing losses at an early age.

The challenge now is to evaluate all aspects of the programme and to recommend how to adapt this hearing screening model to smaller and more isolated hospitals.

External Committees

E Blair. Perinatal Society of Australia and New Zealand (PSANZ) Western Australian sub-committee.

C Bower. Member, National Perinatal Statistics Unit Management Advisory Committee.

C Bower. Member, Scientific Sub-Committee of the Human Research Ethics Committee, Curtin University of Technology.

C Bower. Member, Scientific Review Panel, Australian Paediatric Surveillance Unit, Sydney

C Bower. Member, National Child Health Information Advisory Committee, Australian Institute of Health and Welfare, Canberra.

C Bower. Member, Australian Birth Defects Society.

C Bower. Member, Confidentiality of Health Information Committee, for Health Department of Western Australia.

S Eades. NH&MRC Aboriginal Health Research Agenda Working Group.

S Eades. Trustee, Rio Tinto Aboriginal Foundation.

S Eades. Trustee, Robert Riley Law Scholarships, Australian Youth Foundation.

S Eades. Trustee, Indigenous Medical Scholarships, Australian Medical Association.

J Freemantle. National Secretary, Public Health Association of Australia.

J Freemantle. Chair, Lady Lawley Cottage Management Committee, Australian Red Cross.

J Freemantle. Past President Australian Federation of University Women.

J Freemantle. Executive Committee, Public Health Association of Australia (WA Branch).

J Freemantle. Trustee for Public Health Education and Research Trust.

D Lehmann. Vaccine Impact Surveillance Network committee, WA.

D Lehmann. The Meningitis Centre committee, WA.

D Lehmann. WA Otitis Media Group.

A Read. Editorial Board, Paediatric and Perinatal Epidemiology.

A Read. Member, Data Linkage Project Management Committee, Department of Public Health, The University of Western Australia and Health Information Centre, Health Department of Western Australia.

Staff and Students

Epidemiology

Head

Carol Bower *MBBS MSc PhD FAFPHM DLSHTM
Clinical Associate Professor (The University of
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Janet MacLean *DipSocSc*
Anne Mahony *RN BNurse(Hons)*
Daniel McAullay *RN BSc(Nursing) MAE(Indigenous
Health)*
Angela McHarrie
Karen Moonen
Barbara Moore *BSN MPH*
Kaye Moore

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Suzanne Peel *RN RM*
Anne Read *BSc(Hons) PhD*
Gail Reading *BSc(CompSci)*
Sharon Robartson *RN RM*
Peta Serna *BA(Hons)*
Desiree Silva *MBBS MPH FRACP*
Kerryn Sivwright *BSc(Hons)*
Carolyn Smargiassi
Fiona Smith *NNEB*
Jane Smith *RN*
Fiona Stanley *AC MSc MD FFPHM FAFPHM
MFCCCH FRACP FRACOG FASSA HonDSc*
Mary Tennant *RN RM BAppSci MPH*
Linda Watson
Sally Yong
Jan Zach *BAppSci PostGrad DipHlthSci*

Meningitis Centre

Rozanne Silburn *RN BA*

Students

Kevin Blake *MBBCh CAO PhD* candidate
Mary Carey *BSc DipPubHlth MPH* candidate
Lyn Colvin *BCom MPH* candidate
Maxine Croft *BAppSci PhD* candidate
Glenys Dixon *BA BPsych MPsych(Clin)* candidate
Jan de Groot *RN BAppSci GradDip(Midwifery) MPH*
candidate
Sandra Eades *BMed PhD* candidate
Jacinta Francis *MPH* candidate
Emma Glasson *BSc(Hons) PhD* candidate
Michéle Hansen *BSc MPH* candidate
Seonghee Kwon *BA MPH* candidate
Anne Mahony *RN BNurs(Hons) PhD* candidate
Jan Payne *SRN (UKCC) PGradDip(HlthAdmin)*
MPH candidate

Visitors

Nadia Badawi *MBBCh(Hons) MSc PhD DCH
MRCP(I) FRACP*
Louise Golley *BEC BSc GradDip(Population Health)*
Jennifer Kurinczuk *BSc(Hons) MBChB MSc MD
MFPHM FAFHM DLSHTM*

Publications for the year 2000

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Research Grant Income

Australian Government Grants

Commonwealth Department of Family & Children Services

Social-Emotional Development Continuum.....87,411

National Health and Medical Research Council (Australia)

Genetic epidemiology of complex childhood disease.....62,631

Regulation of the functional phenotype of respiratory tract dendritic cell populations.....276,577

Studies on the immunological mechanism underlying the development of allergic
respiratory diseases.....131,521

Physiological assessment of infant airway and parenchymal mechanics in health and
disease.....153,074

Inhibition of cytokine mediated inflammation in cystic fibrosis67,135

Epidemiology of maternal and child health.....1,155,235

Specific inhibition of leukaemia cell growth by mimetic peptides selected in vivo71,295

House dust mite allergens and antigens in allergic sensitisation.....210,516

Exploring the complexity of the asthma phenotype.....113,489

Cat Allergens: the neglected specificities.....65,232

Effects of upper versus lower respiratory infections on the induction of atopic asthma.....186,235

Mimotopes for the investigation and therapy of allergic disease.....73,155

Regulation of a novel target gene aldehyde dehydrogenase 1, by HOX11 in
childhood leukaemia.....47,239

Socioeconomic risk factors and treatment seeking behaviour for otitis media in the
Aboriginal population of Kalgoorlie-Boulder region.....93,621

Office for Aboriginal and Torres Strait Islander Health

Western Australian Aboriginal Child Health Survey.....825,000

Western Australian Government Grants

Aboriginal Affairs Department

Aboriginal Youth Suicide Prevention Working Party Grant.....40,000

Disability Services Commission

Western Australian Aboriginal Child Health Survey.....5,000

Education Department of Western Australia

Western Australian Aboriginal Child Health Survey.....40,000

Family and Children's Services

Western Australian Aboriginal Child Health Survey.....59,000

Health Department of Western Australia

Mental Health Division.....476,273

Universal Newborn Hearing & Screening Program.....348,000

Western Australian Aboriginal Child Health Survey.....60,000

Healthway

Western Australian Aboriginal Child Health Survey.....50,000

Prenatal and perinatal antecedents.....100,000

Risk factors for otitis media.....100,000

Investigating early causal pathways of mental health problems.....99,132

Homeswest	
Swimming Pools Project.....	29,644
Office of Youth Affairs	
Western Australian Aboriginal Child Health Survey.....	15,000
WA Drug Abuse Strategy Office	
Report on Youth Suicide in Western Australia including Cannabis and other drugs.....	25,016
Other Peer-reviewed Grants, Scholarships and Fellowships	
Asthma Foundation of Western Australia	
Inhaled glucocorticoids: Impact on alveolar and maturation in early postnatal life.....	33,587
Child Health Research Foundation	
Child Health Research Foundation Medical Research Fellowship.....	15,802
Indigenous Child Health Research Network.....	82,000
Children’s Leukaemia and Cancer Foundation	
Leukaemia & Cancer Research triennial block grant.....	195,446
Children’s Leukaemia and Cancer Research Foundation/Three Boys Legacy	
Maintenance for research into brain tumours.....	17,883
Financial Markets Foundation	
The epidemiology of Rett Syndrome in Australia.....	35,000
Garnett Passe and Rodney Williams Memorial Foundation	
Universal Newborn Hearing & Screening Program.....	102,985
Lotteries Commission	
Western Australian Aboriginal Child Health Survey.....	198,883
Medical Research Fund of Western Australia (MEDWA)	
The impact of inhaled corticosteroids on alveolar formation and maturation in early postnatal life.....	35,000
National Institutes of Health (USA)	
Specific peptide inhibition of oncoprotein interactions.....	131,642
Molecular genetic lesions & clinical outcome in ALL.....	156,228
Commercial Grants and Contracts	
ALK Pharmaceuticals	
Experimental desensitisation to inhalant allergens.....	83,062
Glaxo Wellcome Pty Ltd	
Immunoregulation in allergy and atopic dermatitis.....	423,000
Asthma Genetics.....	283,746
Other Grants	
International Rett Syndrome Association	
The epidemiology of Rett Syndrome in Australia.....	9,866
Rio Tinto	
Western Australian Aboriginal Child Health Survey	30,000
Variety Club of Western Australia	
Research Fellow in Brain Tumour Research.....	50,000
TOTAL	6,950,561

Administration and Corporate Services

Robert Ginbey



Overview

A number of significant corporate projects came to fruition in year 2000.

New building relocation: The move to the new building was undertaken in February/March. That the relocation went smoothly reflected the careful planning of the project leaders Nino Gullotti and Thierry Venaille and the full cooperation of the respective research teams. The operation of the new building was not without teething problems, most of which have now been rectified.

Goods and Services Tax (GST): The preparation for the introduction of the GST required a dedicated effort by the Finance and Accounts staff. Various changes have been required in reporting and financial systems impacting on the Institute as a whole and on the specific purpose charitable fundraising activities.

Management Information System (MIS): A new management information system has been in planning for some years. The various options were put on hold during the frenetic years of planning and construction of the new building. As the new building become fully operational, the MIS was again identified as a high corporate priority. The MIS represents a major investment for the Institute. The project leaders, Toby Harrison, and Nino Gullotti, along with other senior administrative staff have been required to spend long hours in planning and implementation alongside the consultancy firm selected to provide the new integrated systems. Through the dedicated attention of the human resources section staff Julia Emmerson and Leanne Scott, by December 2000 the new payroll and human resources system was on line. The finance, accounts and purchasing system will follow in 2001 and then the facilities management system later in the year.

New Building Official Opening: The formal celebrations were held on 1 September 2000. The planning for the celebrations was undertaken by a team of administrative staff and coordinated by Ian Lilburne from the University of Western Australia. We were delighted to be able to accommodate over 600 guests in the building and by means of audiovisual technology to ensure that everyone had the opportunity to see and to hear the full proceedings. We were also delighted that so many were able to stay on after the formal proceedings to enjoy the festivities. Development Office staff, Naomi Mellish and Tammy Gibbs, the Directorate staff, Natalia Bilyk and Colleen Moylan, and the Building Management staff, Thierry Venaille and Andrew Morup all contributed to a very successful function.

With the guidance of Bruce McHarrie, the newly appointed Chief Financial Officer, the respective managers of the administrative sections have been able to develop a more devolved corporate decision making structure. This has enhanced their status and

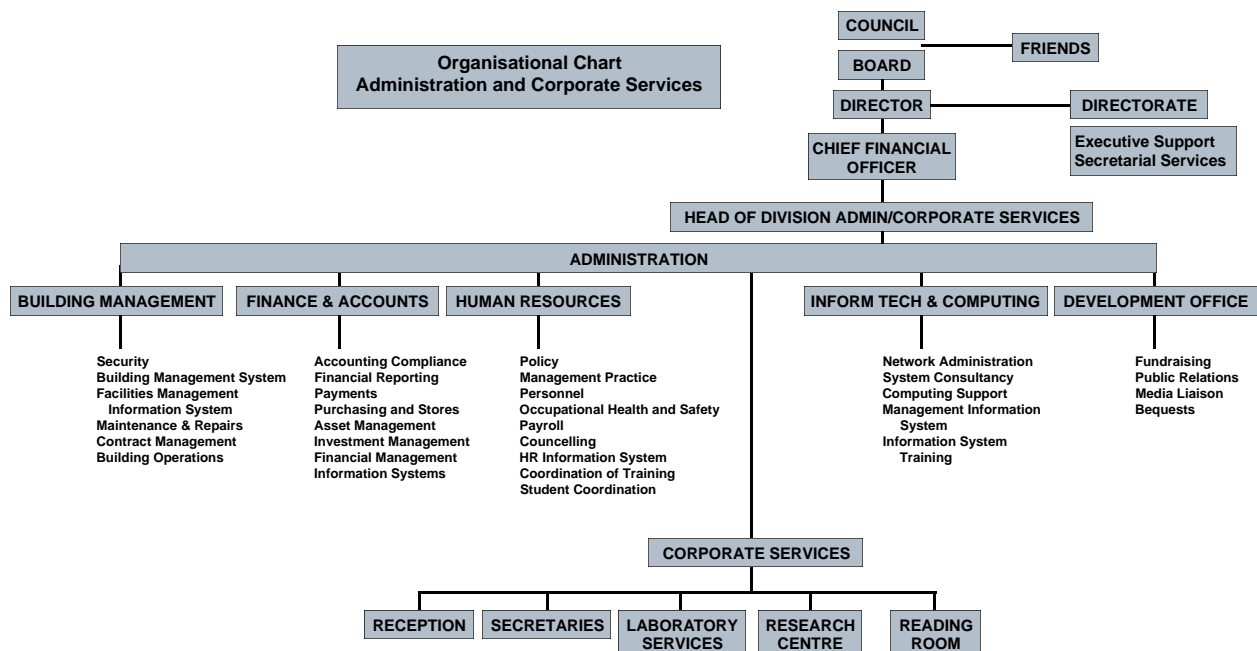
confidence as business managers. Each manager is now much clearer on areas of accountability, responsibility, and decision making. There has also been a focus on effective communication and customer service, and the professional development and growth of all administrative and corporate services staff.

The corporate decision making process has been enhanced also by the effective operation of staff committees, each with its own terms of reference related to administrative services. These are the Human Resources Reference Group, the House

Committee, the Occupational Safety and Health Committee and the Information Technology Reference Group.

Preparations are now under way for the major five yearly international review of the Institute, which will take place in December 2001. The Institute Scientific Advisory Committee, with the support of an Institute working party will guide this.

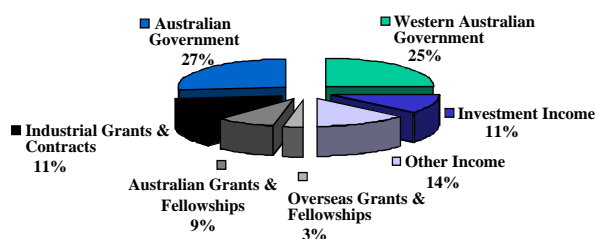
Robert Ginbey



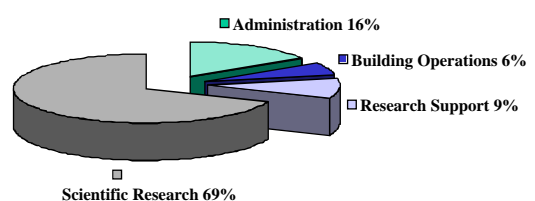
The Year in Brief

	2000	1999	% Change
Expenditure	12,297,727	8,895,241	38.25%
Number of Staff	229	148	54.73%
Number of Visiting Scientists	24	14	71.43%
Number of PhD Students	28	31	-9.68%
Total	241	193	5.60%

Income \$11.2 million



Expenditure \$12.3 million



Staff

Head of Administrative Division

Robert Ginbey *BA BEd GradDipPSMgt MACE*

Building Management

Thierry Venaille *PhD* (Manager)

Andrew Morup (from May)

Development Office

Naomi Mellish (Manager)

Tammy Gibbs *BComm*

Kaye Webse (Volunteer)

Directorate

Natalia Bilyk *BSc(Hons) PhD*

Colleen Moylan

Finance and Accounts

Antonino Gullotti *BBus* (Manager)

Claudja Backory

Tricia East (from August)

Lisa Kenchington (from October)

Kim Law *BBus(Acct)*

Amanda Marsh *Bsc(Hons)* (until October)

Human Resources

Julia Emmerson *BSc(Hons)Psych* (Part time)

(Manager)

Karen Krska *DipAppSci DipBus(Acct)* (Part time)

Leanne Scott (Part time)

Information Management

Barbara Moore *BSN MPH* (Part time)

Lin Strauss (Part time)

Information Technology and Computing Support

Toby Harrison *B.Comm BEng (Hons)* (Manager)

Jean-Paul Blaquiére (Casual) (from November)

Glenn Butcher

Sophie Divliaev *BSc* (Part time)

David Lewis *BAppSc*

Laboratory Services

Mark Brunini

Mirella Burgum (Part time)

Sarah Hagger

Lisa Kenchington (Part time) (until October)

Sue Lenzo (Casual)

Jan Peek (Part time)

Evan Roeterdink (Casual) (from October)

Reception

Anne Davis (Part time) (from May)

Penny Duff (Part time) (until February)

Jacinta Johnston (Part time) (until May)

Verity Wright *BA(Hons)* (from February)

Scientific Secretaries

Anne Amourgis

Susan Davies *Bsc (Hons)* (from November)

Jackie Goldfinch (from March)

Helen Howells (Part time)

Reinette Orr (Part time)

Janet Parsell (Part time) (until November)

Occupational Health and Safety

Occupational Health and Safety covers a broad range of workplace issues which may relate to the workplace itself, the work undertaken, and the staff and students who are involved in or affected by work activities. In the year 2000 the Institute consolidated the position of OHS Coordinator. This role includes the functions of:

- Organising and reporting the monthly OHS meetings, attended by staff representatives from each Division;
- Implementing training in areas such as manual handling, first aid and fire safety;
- Compiling an OHS Induction Package for new staff so that they have ready access to relevant safety information.

Other OHS initiatives being addressed include:

- Up-dating of the existing Institute Safety Manual to reflect the move to the new premises;
- The introduction of a central register for the hazardous substances used by the laboratories; and
- To raise the level of workplace OHS awareness so that the institute can continue to offer a high standard for its staff and visitors.

The Meningitis Centre

Throughout 2000, the Meningitis Centre continued to consolidate its public work with the ongoing support of patron sponsor, the National Australia Bank and also from our valued members and donors.

The aims of the Meningitis Centre; to provide information and support services to families affected by meningitis, to improve public awareness and to foster research into meningitis have been well served by a number of initiatives throughout the year. The Centre's fridge magnets, which outline meningitis symptoms in infants and adults, continue to be a major vehicle for raising awareness in the community. With assistance from Sigma, the magnets reach the community via Amcal and Guardian pharmacies. The Centre also distributed magnets and pamphlets in response to public requests for information. The Health Department of Western Australia distributed over 10,000 magnets to Child Health Centres throughout the State.

The Centre's information brochure, "*The Facts About Meningitis*", was updated with assistance from Health West.

To coincide with the peak season for bacterial meningitis, the Meningitis Centre coordinated a highly successful media campaign from July through to September. A series of advertisements outlining the signs and symptoms of meningitis in infants and adults were placed in newspapers throughout the State. The response from this year's seasonal campaign was far greater than in previous years.

The Meningitis Centre continued to coordinate quarterly Family Support gatherings throughout the year.

A successful fundraising campaign was conducted in the lead-up to Christmas, with The Centre selling Christmas cards, which featured the artwork of Hollee West, who died at the age of 20 after contracting bacterial meningitis.

There were some significant developments during the year with regard to the surveillance of meningitis. Invasive pneumococcal disease became a notifiable disease, with the Health Department of Western Australia taking over surveillance. With this change the Meningitis Centre's Vaccine Impact Surveillance Network (VISN) moved its emphasis to meningococcal disease. The Medical Council invited representatives from the Meningitis Centre to join its Meningococcal Working Party. Year's end also saw the departure of our long-serving co-ordinator, Ms Rozanne Silburn, after nearly nine years of valuable work for the Centre.

Planning for 2001 includes extending the Centre's influence nationally by developing a network of Centres.

Management Committee

Bruce Langoulant – Chairman
Robert Ginbey
Dr Jag Gill
Sarah Johnston
Michael Kailis
Dr Tony Keil
Dr Deborah Lehmann
Dr Tony Watson
Rozanne Silburn - Coordinator

Donors to Meningitis Centre in 2000

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Mr A Ventouras
BG Young
DM & LM Watson
Mr and Mrs N Winley
Mr and Mrs F & W Zuideveld

Friends of the Institute



Josephine Spaul and Marilyn Stewart (Friends President)

2000 was an exciting year for the Friends of the Institute. Friend-raising was expanded into regional Western Australia whilst fresh fundraising initiatives proved to be successful. The Friends continued to support the research at the Institute with some significant contributions to the projects and studies.

In 2000, the Perth committee held three events. On June 13, Friends supporters were invited to the Institute for a tour of the building followed by afternoon tea with committee members. The Friends inaugural ladies golf day was held on September 11 at Cottesloe Golf Club with around 100 ladies enjoying a round of golf and lunch. The golf day was such a huge success that another is already planned for 2001. The final event on the calendar was the annual Christmas Brunch. Past brunches have been held at the home of patron Angela Bennett but was this year held at the new Institute building, to give guests the chance to see the Institute and to give the Bennetts a well deserved rest.

The Friends were also active in the country areas of Western Australia. The Margaret River committee held an information day and a raffle to inform locals of the presence of the Friends and the work of the Institute. An art auction was held at the Melting Pot Glass Studio in Margaret River with works from local artists being auctioned to a crowd of more than 200 people. The committee also benefited from the open garden scheme, as President Deborah Jacob opened her gardens to raise money for the Friends of the Institute. A group of ladies from Kojonup held a luncheon for 120 people on September 22 in the beautiful garden of Joyce Reid. As a result of this luncheon, a small group has formed a Friends committee with the view of educating the community about child health issues.

The Friends were delighted to have the support of the Bridgetown community in 2000. Josephine Spaul held her annual "Children Helping Children" Christmas concerts and chose to donate half of the proceeds to the Friends. The Friends also benefited from a fresh produce stall, organised by Janice Kelly, at the Bridgetown Show.

These events have enabled the Friends to assist the Institute in many ways. Computer software for the analysis stage of birth defects research; a medical dictionary and Immuno-Assay Handbook; a lap top computer for the Rett Syndrome study as well as sponsorship of the Rett Syndrome information evening and their attendance at the Neurological Expo; provision of a training session for the Clinical Sciences division to use their Image Pro Image Analysis System; and funding to the RASCALS study for them to provide pens to their participants.

The Friends farewelled patrons, Major General Michael Jeffery and Mrs Marlena Jeffery, when they left Western Australia during 2000. However, Western Australia's new Governor, Lieutenant General John Sanderson and his wife Lorraine, were more than happy to join the Friends as patrons. We welcome them and look forward to 2001 with our new patrons.

Committee members serve on a voluntary basis and bring a multitude of different skills and experience to make the Friends an important part of the Institute. Committee members have changed throughout the year and we would like to thank past and current members for their support and commitment. In particular, special thanks must go to Mrs Rae Willis who served as President of the Friends and as an Institute Board member until September. Mrs Marilyn Stewart has filled this role since September. Committee members throughout 2000 include:

Perth - Rae Willis (President to September), Marilyn Stewart (President from September), Sue Bolto, Lyn Buchan, Kathryn Carr, Lois Egerton Warburton, Jenny Elphick, Noela George, Tammy Gibbs, Robert Ginbey, Jennifer Grove, Vicki Haunold, Anne Hector, Naomi Mellish, Ursula Prince, Nanette Robson, and Fiona Wildy

Margaret River - Jenny Booth (President to September), Deborah Jacob (President from September), Jamie Ashton, Jim Boyd, Aileen Budge, Pat Gray, Lynley Madson, Madeleine Miles, Sarah Moore, Nikki Newton, Jan Smith and Colleen Wild.

Giftgiving Opportunities

Giftgiving Opportunities

“Medical research is expensive - but disease is even more expensive. It costs our community millions of health care dollars every year, it costs families heartache and pain and it still costs too many young lives.”

Professor Fiona Stanley AC

The Development Office was established primarily to secure research support funding. The Institute has a proven track record in attracting peer-reviewed research grants but unfortunately these grants don't fully cover the cost of conducting research. For instance, every research grant received requires laboratory space, support personnel, equipment acquisition and replacement and administrative support.

There is no doubt that our donors are making a significant contribution to the functioning of the Institute, and by doing so they enable our scientific teams to carry out the very best research possible under the very best conditions available. This research translates directly into improved health policy, improved health care practices, improved treatment and most importantly, improved prevention rates.

If you are interested in supporting the work of the Institute please ring the Development Office on (08) 9489 7962 or consider the options below:

Tax Deductible Gifts and Pledges

If you would like to make a cash donation you can do so by either visiting the Institute or by mailing a cheque, made out to TVW Telethon Institute for Child Health Research, to PO Box 855, West Perth WA 6872.

Gifts can be made as a once-only payment or can be pledged over a period of time chosen by you.

Bequests

A bequest is a gift made through your will and is worded to suit your wishes. Sample wording is given below and we recommend that you seek the advice of a solicitor to ensure that your bequest is clearly and legally stated.

I give to the TVW Telethon Institute for Child Health Research the sum of

\$..... to be applied for the purposes of the Institute.

If you have already made your will and would now like to provide for the Institute, this can be done by adding a Codicil. A Codicil is an amendment to your will which adds the bequest to it. The Institute has a solicitor who will help you make your codicil, free of charge.

Gifts with Assured Income

Gifts may be made of money or assets with the income from the property retained by the donor during his or her lifetime. Similarly, property can be given to the Institute, with the donor retaining lifetime enjoyment of it.

Discretionary Trusts

When establishing a trust fund for the benefit of your family, you can include a charitable organisation as a potential beneficiary of the trust. This allows the allocation of trust income to the Institute, with all the resulting tax concessions, in years when family circumstances make it appropriate.

Tribute Gifts

This is a gift that is made in the name of friends or family members. "In honour" donations include special occasions such as a birthday, anniversary, wedding, Christmas or any other occasion special to you. "In memory" donations honour the deceased and their family with a lasting and worthwhile gift that may be made in lieu of flowers.

Donor Acknowledgement

Donor Acknowledgement

Hope is a precious gift. We would like to sincerely thank the following individuals, clubs, corporations, schools and groups for helping us bring hope to the lives of countless children and their families. Your support is, as always, greatly appreciated.

Our supporters are

Bequests:

The late Mrs Margaret Lillie
The late Hilda Mary Eileen Aylmore
The estate of the late Arthur and Belle Watson
The late Mrs Anna Maria Motroni
The late Geoffrey Francis Sutcliffe
The J P Stratton Trust

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 Armadale Primary School
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 Clifton Hills Primary School
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 Newton Primary School
 Pegs Creek Primary School
 Perenjori Primary School

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And all the Friends Committee members who contribute.

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who choose to remain anonymous.*