



Menzies School of Health Research
Northern Territory Australia

1997-98 Annual Report
and
3rd Quinquennial Review

Volume II

- **Unit Reports**
- **Publications 1993 - July 1998**

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VOLUME II

MSHR Unit Reports (1993 - July 1998)

**[Reference Nos] in square brackets refer to
MSHR Publications at the back of this Volume
(from page 110)**

TABLE OF CONTENTS

ADMINISTRATION AND FUNDRAISING.....	1
STAFF IN ADMINISTRATION	1
FUNDRAISING	2
FINANCIAL SYSTEMS	2
AWARD/AGREEMENT	3
COMPUTING AND BIOSTATISTICAL UNIT.....	4
COMPUTING.....	4
BIOSTATISTICS.....	5
SIGNIFICANT COLLABORATIONS	5
LABORATORY SERVICES.....	6
PURCHASING.....	6
SAFETY	6
LABORATORY TRAINEES	7
COMBINED HEALTH BUILDING.....	7
FUTURE DIRECTIONS.....	7
ABORIGINAL POLICY AND HEALTH EDUCATION UNIT	8
1. CULTURAL AWARENESS PROGRAMS.....	8
2. CAREER STRATEGY.....	9
3. RESEARCH	9
<i>Broad Objectives - Menzies School of Health Research.....</i>	<i>10</i>
<i>Specific Objectives - Aboriginal Policy and Health Education Unit.....</i>	<i>10</i>
PROJECTS	10
<i>Rethinking Compliance.....</i>	<i>10</i>
<i>Rheumatic Fever Prevention.....</i>	<i>11</i>
<i>STD Prevention</i>	<i>11</i>
<i>Kava, Alcohol and Their Effects</i>	<i>11</i>
<i>Otitis media - Randomised Clinical Trials</i>	<i>11</i>
<i>Indigenous Health and Education - Exploring the Links</i>	<i>11</i>
<i>Laboratory Work</i>	<i>11</i>
CENTRAL AUSTRALIAN UNIT	13
ADMINISTRATIVE AND OTHER SUPPORT FACILITIES	13
PROJECTS COMPLETED SINCE THE LAST REVIEW	15
<i>Adult Health Surveys in 3 Aboriginal Communities in Central Australia</i>	<i>15</i>
<i>Central Australian Aboriginal Alcohol Program Unit (CAAAPU) Evaluation.....</i>	<i>15</i>
<i>Health Care Expenditure in NT Remote Health Services</i>	<i>15</i>
<i>Community Involvement in Health Services for Indigenous Peoples.....</i>	<i>16</i>
<i>Optional Standards of Care for Frail Aged Aboriginal People.....</i>	<i>16</i>
<i>Community Control of Aboriginal Health Services in the Northern Territory.....</i>	<i>16</i>
<i>Evaluation of Diabetes Control Activities in Central Australia.....</i>	<i>16</i>
<i>Evaluation of Tri-State STD/HIV Project.....</i>	<i>17</i>
<i>Review of Northern Territory Government Remote Health Services in Central Australia</i>	<i>17</i>
<i>Ambulatory Care Project (Part C) : An Analysis of Models of Remote Area Health Service Delivery in the Northern Territory.....</i>	<i>18</i>
CURRENT PROJECTS	19
<i>An Evaluability Assessment of Central Australian Mental Health Services</i>	<i>19</i>
<i>Evaluation of Central Australian Aboriginal Congress Community Health Program</i>	<i>20</i>
<i>Evaluation of the "Wise Use of Medicine" Project.....</i>	<i>20</i>
<i>Developing a Preventive Approach to Nutrition Problems in a Remote Community.....</i>	<i>20</i>
<i>Improving Management in a Cross Cultural Context</i>	<i>21</i>
<i>CRC Cross-Cultural Education and Research Program.....</i>	<i>21</i>
OTHER ACTIVITIES.....	21

THE FUTURE	22
CLINICAL UNIT	23
INFECTIOUS DISEASES.....	23
<i>Antibiotic Guidelines and Treatment Protocols</i>	23
<i>Melioidosis and Pneumonia</i>	23
<i>Scabies</i>	24
GROUP A STREPTOCOCCAL DISEASES.....	24
<i>Acute Rheumatic Fever and Rheumatic Heart Disease</i>	25
<i>Rheumatic Fever Information Package</i>	25
<i>Acute Post-Streptococcal Glomerulonephritis</i>	26
<i>Streptococcal Pyoderma and Scabies</i>	26
<i>Towards a Group A Streptococcal Vaccine</i>	26
<i>Invasive Group A Streptococcal Diseases</i>	27
OTHER INFECTIOUS DISEASES	27
SUBSTANCE ABUSE.....	27
OTHER SERVICE DELIVERY STUDIES.....	29
THE ABORIGINAL BIRTH COHORT STUDY.....	29
<i>Community Feedback</i>	31
<i>Future Directions</i>	31
TOXINOLOGY & TOXICOLOGY	31
<i>Bush Medicines</i>	31
<i>Snakebites</i>	32
<i>Jellyfish</i>	33
<i>Manganese and the Groote Eylandt study</i>	34
INTERNATIONAL HEALTH.....	35
<i>Studies of Clinical Epidemiology of Malaria and New Methods of Diagnosis</i>	35
<i>Nitric Oxide (NO) in Severe and Uncomplicated Adult Malaria</i>	36
<i>S-Nitrosothiols and Malaria : Potential Disease-Modifying Effects</i>	36
<i>Tuberculosis Drug Resistance in Timor</i>	37
<i>Other Work</i>	37
<i>Significant Collaborations</i>	37
EAR HEALTH AND EDUCATION UNIT	39
MEDICAL ASPECTS OF DISEASE.....	39
<i>Antibiotic vs Placebo for Prevention of Chronic Otitis Media</i>	40
<i>Chronic Suppurative Otitis Media (CSOM) - Can Compliance be Improved?</i>	40
<i>Investigation of Otitis Media and Pneumococcal Carriage in Child Care Centres</i>	41
MICROBIOLOGICAL ASPECTS OF DISEASE : "EARLY, MULTIPLE, DENSE & RESISTANT".....	42
<i>Neonatal Acquisition of Respiratory Bacterial Pathogens and Onset of Persistent Otitis Media</i>	42
<i>Treatment of Otitis Media</i>	43
<i>Understanding the Endemicity of Respiratory Bacterial Infection</i>	43
<i>Antibiotic Resistance</i>	44
<i>Models for Endemic Carriage of Multiple Strain Organisms</i>	45
<i>Haemophilus influenzae</i>	45
<i>Hib Carriage Increase</i>	45
AUDIOLOGICAL ASPECTS OF DISEASE.....	45
<i>Masking Level Differences : Normative Values</i>	45
<i>The use of Late Evoked Potentials to Determine Conductive Hearing Loss</i>	46
<i>AB Word Lists : Normative Values</i>	46
<i>Early-Onset Auditory Deprivation and Central Processing Disorders in Aboriginal Children</i>	47
<i>Advancing Indigenous Literacy through Support for Hearing Disabilities</i>	47
CROSS CULTURAL HEALTH CARE CHALLENGES	48
<i>Health Communication</i>	48
<i>Compliance/Adherence Issues</i>	49
<i>Informed Consent</i>	49
<i>Hearing Loss within the Justice System</i>	49
<i>Best-Practice Models in Medical and Habilitative Services</i>	50
<i>Guidelines for OM for Indigenous Australians</i>	51



BIOMEDICAL ENGINEERING PROJECTS.....	51
<i>Air Pressure Monitoring System with Video-Pneumatic Otoscopy</i>	51
<i>Using Microprocessors for Compliance/Adherence Monitoring</i>	52
<i>Noise Level Monitor for Public Health Education</i>	52
OTHER COLLABORATIVE RESEARCH INITIATIVES.....	52
<i>Territory Health Services</i>	52
<i>Australian Hearing Services</i>	52
<i>World Health Organization</i>	53
FUTURE DIRECTIONS AND SUMMARY.....	53
HEALTH SOCIAL SCIENCES UNIT.....	54
ALCOHOL MISUSE AND VIOLENCE.....	55
COMMUNITY-BASED PUBLIC HEALTH INITIATIVES TO REDUCE ALCOHOL-RELATED HARM.....	56
KAVA.....	59
EVALUATION.....	60
LINKS WITH THE COOPERATIVE RESEARCH CENTRE.....	61
MPH PROGRAM.....	61
POSTGRADUATE RESEARCH STUDENTS.....	61
FUTURE DIRECTIONS.....	61
MOLECULAR GENETICS UNIT.....	62
STREPTOCOCCUS PYOGENES.....	62
<i>Novel Typing Method for GAS</i>	62
<i>Mechanism of Antigenic Diversity of M Protein</i>	63
<i>Molecular Genetics of S. pyogenes</i>	65
<i>S. pyogenes - Tissue Tropism and Primary Site of Infection for Invasive Diseases</i>	65
<i>S. pyogenes and Chronic Renal Disease</i>	65
<i>Streptococcal Inhibitor of Complement (SIC)</i>	66
<i>Seroconversion to Streptococcal Products</i>	67
<i>Funding</i>	67
<i>Future Directions</i>	68
CHLAMYDIA.....	69
<i>Studies on Gene Regulation in Chlamydia</i>	69
<i>Studies on Novel Surface Proteins</i>	70
<i>Funding</i>	71
<i>Future Directions</i>	71
OTHER CONTRIBUTIONS.....	71
ACKNOWLEDGMENTS.....	72
MOLECULAR PARASITOLOGY UNIT.....	73
MALARIA.....	73
<i>Identification of clag, a Gene Required for Cytoadherence</i>	73
<i>Clag is Not Alone : The clag Gene Family</i>	74
<i>Future Directions</i>	75
<i>Funding</i>	75
SCABIES.....	76
<i>Are Sarcoptes scabiei Mites on Humans and Dogs in Aboriginal Communities the Same or Different Populations?</i>	76
<i>Community Feedback</i>	77
<i>Future Directions</i>	77
<i>Funding</i>	77
HAEMOPHILUS INFLUENZAE.....	78
<i>Molecular Epidemiology of Haemophilus influenzae</i>	78
<i>Hib in the Northern Territory</i>	78
<i>Community Feedback</i>	79
<i>Future Directions</i>	79
<i>Funding</i>	80
DONOVANOSIS.....	80
<i>A Non-Invasive Diagnostic Test by PCR</i>	80

<i>Future Directions</i>	81
<i>Funding</i>	81
OTHER WORK.....	81
SIGNIFICANT COLLABORATIONS.....	81
PUBLIC HEALTH AND EPIDEMIOLOGY UNIT	82
SOCIAL AND BIOLOGICAL ORIGINS OF POOR ABORIGINAL HEALTH.....	83
<i>Maternal and Infant Health</i>	84
<i>Bacterial Infection</i>	84
<i>Alcohol and Cigarettes</i>	85
<i>Health Services</i>	85
<i>How Long For Aboriginal Health to Improve?</i>	87
ABORIGINAL MORTALITY : A CULTURAL AND EPIDEMIOLOGICAL APPROACH.....	87
<i>Community Responses to Unexpected Deaths</i>	87
<i>A Language to Improve Communication</i>	88
<i>Public Health Audit of Adult Aboriginal Deaths</i>	88
<i>Study of Forensic Autopsy Data</i>	88
<i>Mortality amongst Diabetic Aboriginal People</i>	89
<i>Accuracy of Death Certification</i>	89
<i>Emergent Issues</i>	89
<i>Mortality Patterns and Potential Years of Life Lost</i>	90
ABORIGINAL GROWTH AND NUTRITION.....	90
<i>Minjilang and Related Projects</i>	90
GROWTH AND BODY SIZE IN INDIGENOUS AUSTRALIANS.....	91
<i>Body Size in the NATSI Survey</i>	91
<i>Analysis of 10 Years of Growth Data from the Katherine Region</i>	93
<i>Community Feedback and Future Directions</i>	94
EVALUATION OF THE PILOT PHASE OF THE STRONG WOMEN, STRONG BABIES, STRONG CULTURE PROGRAM.....	94
<i>Community Feedback and Future Directions</i>	95
INFECTIOUS DISEASES.....	95
<i>Hepatitis B Virus Infection</i>	95
<i>HTLV-I Virus</i>	96
<i>Diagnosis and Treatment of Donovanosis</i>	96
<i>The T-test and PCR to Diagnose Genital Infections</i>	96
<i>New Strategies for Trachoma Control</i>	97
<i>Epidemiology of Group A Streptococcal (GAS) Infection</i>	98
MODELLING OF INFECTIOUS DISEASE PROCESSES.....	98
<i>EPIMOD Computer Package</i>	99
<i>Modelling of Onset of Ear Infections (Otitis Media)</i>	100
<i>Endemicity of Respiratory Bacteria</i>	100
<i>Model for Multiple Strain Carriage in Endemic Populations</i>	101
<i>Endemic Model for C. pneumoniae</i>	102
<i>Models for Age Distribution of Post-Infective Disease</i>	103
<i>Proteinuria has an Earlier Age of Onset in those with GAS Antibodies</i>	103
THE NUSA TENGGARA TIMUR PROJECT.....	104
OTHER WORK.....	104
PUBLIC HEALTH EDUCATION.....	105
RENAL UNIT	106
EDUCATION AND SERVICE PROVISION.....	106
END STAGE RENAL REGISTRY (ESRD).....	107
THE COMMUNITY STUDY OF THE EPIDEMIOLOGY OF RENAL DISEASE.....	107
FAMILY HISTORY STUDY.....	108
RENAL ULTRASOUND STUDY.....	108
THE RENAL AND CARDIOVASCULAR-PROTECTIVE TREATMENT PROGRAM.....	108
EVALUATION OF THE TREATMENT PROGRAM.....	108
EVALUATION OF RENAL MORPHOLOGY AND GLOMERULAR SIZE AND NUMBERS.....	109
PUBLICATIONS	110

Administration and Fundraising

Katherine Henderson

In the last five years the School has grown and formed affiliations with NTU, Flinders University and the CRC, all of which have placed new demands on The School's administrative functions. Staff numbers have increased steadily to the current level of 100 EFT. The School operates on a base grant from the Northern Territory Government which has not increased in real terms since the School opened in 1985, and relies for most of the rest of its funds on research grants and fundraising. The major source of grant funded research is the NHMRC. However the NHMRC grants do not cover overhead and administrative costs. Further, in the 1998 funding round, the NHMRC imposed a 10% cut on all but one of the grants to the School.

Menzies School of Health Research has undertaken a major initiative in establishing the MPH program, partly supported by the Commonwealth Department of Health and Family Services' Specialty Programs grant. Again, this area is not fully funded and requires additional support from Menzies School of Health Research' limited base funds.

STAFF IN ADMINISTRATION

The Business Manager, Katherine Henderson, is responsible to the Director and Governing Board for Policy Development and the administrative functions of the School. In 1998 Katherine has had the assistance of Ms Leah AhMat, CRC Trainee in Administration.

Yolanda Jackson is Finance Manager for the Menzies School of Health Research and the Cooperative Research Centre. As such, she is responsible to the Director, and reports to the Finance and Audit Committees for management of School and CRC funds. She is also responsible for ensuring grant funding is properly administered and liaises with research staff and funding bodies to ensure all financial requirements are met.

Margarita Bassett, as Accounts Officer, is responsible to Yolanda for undertaking data entry into the School's computer-based accounting system, checking and processing of payments, production of debtors invoices, and is custodian of the petty cash. Margarita also advises staff on purchasing matters, and provides back-up support to the payroll officer as required. She is also Fire Zone Warden, responsible for staff occupying "The Head" and, for this task, she gets to wear a red hard-hat!

Catheryn Young, as Personnel Officer, is responsible for induction of new staff, payroll and superannuation activities. Catheryn is also Chief Fire Warden for the School and, as such, is a member of the School's Safety Committee.

Debra Davis, as Secretary to the Director, provides essential support in the form of managing his day-to-day activities, registering and prioritising incoming correspondence,

typing and formatting of outgoing correspondence and research papers, and organisation of the Director's travel.

Liz Stubbs, as Academic Administrator, is responsible for overseeing the enrolment of graduate and postgraduate students of the School. Liz handles all student enquiries and liaises with the relevant institutions through which the students are enrolled. She also provides administrative advice and assistance to coursework coordinators and lecturers as required. Until this year, Liz was responsible for assisting staff in applying for grant funding. She is also secretary to the Joint Institutional Ethics Committee of the Royal Darwin Hospital and Menzies School of Health Research.

As Education Assistant, Audrey Langlands assists with the administration of the MPH/DPH Coursework Program. This includes liaising with coursework lecturers and students throughout the academic year.

Gabrielle Falls is the School's Administration Officer in the areas of publications and public relations. In this role Gabby is responsible for production of the School's Annual Report, Occasional Papers and Newsletters; and maintenance of School publications, mailing list and grant support databases. Gabby also assists research staff with the production of grant applications and it is in this capacity that she has been nominated a member of the NHMRC GrantNet User Reference Group. Gabby also provides administrative support to the Deputy Director, Professor David Kemp.

Tracey Burke joined the administrative staff in April 1998 as receptionist and travel agent! Tracey's duties require her to track staff movements and handle any travel and accommodation bookings required by School staff, from field trips to attendance at International conferences. She is also responsible for maintaining stationery levels and registering incoming and outgoing cheques.

Lindy Warrell joined the staff in July 1998 as Executive Officer and Personal Assistant to the Director. Lindy will assist John Mathews in various aspects of the management of the School and the CRC, including fundraising and public relations. With her background in Anthropology, Lindy will also be instrumental in promoting improved communications, understanding and cooperation between the diverse research and academic interests represented at the School and between indigenous and non-indigenous interests both within and outside the School.

The Office Manager in Alice Springs is Jackie Parkinson, while Cathy Hampton provides office support. Their responsibilities are discussed in the Central Australian Unit report.

FUNDRAISING

The School faces the dilemma that increased activity in its two areas of core business, research and education, steadily contribute to its impoverishment.

The School has engaged Downes Venn Associates to develop a fundraising strategy seeking corporate sponsorship to offset this. It is expected that this will be progressively implemented in 1999 and 2000.

FINANCIAL SYSTEMS

Over the last five years The School's growth in size and complexity has been met by the introduction of more sophisticated financial management and reporting systems. In 1997,

Menzies School of Health Research took on the role of agent for the Cooperative Research Centre, responsible for financial management and other areas of administration such as Information Technology. At this time the position of Finance Manager was introduced, for both Menzies School of Health Research and the CRC. Mrs Yolanda Jackson, a qualified accountant, was employed to fill this position.

The goals of Menzies School of Health Research financial reporting systems are :

- transparency in reporting;
- timely reporting to the Board, the Chairman, the Director and the Finance Committee;
- data input in a form which allows speedy acquittal against the many grants and to meet the idiosyncratic acquittal requirements of different agencies. (Menzies School of Health Research acquits to many organisations against at least 40 different sets of acquittal requirements. At least one Commonwealth department requires a different form of acquittal on each separate grant.);
- budget and expenditure reports at appropriate decision-making levels, (eg. for chief investigators on grants);

To support these aims the following have been introduced :

- Financial data is prepared monthly on an accrual basis, matching income and expenditure, allowing comparison of performance month by month and against the equivalent period in the previous financial year.
- Quarterly reports comparing actuals against budgets are provided to the Board and the Finance Committee.
- Budgets are produced twice each year to include a revision and review of the financial year plan in the light of NHMRC grants, usually determined by November.
- Chief investigators are now supplied with a financial report on each of their grants.
- Acquittal time lag has been reduced to nil. NHMRC received their December 1997 acquittals before they had sent out the forms!
- A new system has been introduced to ensure timely claims against all debtors.

In each of the last five years Menzies School of Health Research has had unqualified audits. Installation of a new software accounting package is planned for 1999 which will:

- provide for improved data integrity;
- provide more user friendly data input;
- provide more versatile reporting formats;
- provide easier administration of travel, which is a major activity at Menzies School of Health Research;
- eliminate any year 2000 difficulties.

AWARD/AGREEMENT

The School has, over an extended period, been engaged in discussions about the introduction of a Menzies School of Health Research Award.

Legislative change has overtaken the School in its deliberations and it has now been decided that the most sensible approach is to develop an Agreement to be registered with the Industrial Relations Commission. It is expected that the Agreement will be in place this year.

Computing and Biostatistical Unit

Abron Lukitsch

The aim of the Computing and Biostatistical Unit is to provide a high level of support and service to the School in Information Technology. The Unit collaborates with all of the School's other Units and with many external core partners.

Support is provided for projects from the early stages of data collection, through analysis and the dissemination of the information and results. Provision to achieve this through various mediums requires a good infrastructure and a system that allows efficiency, reliability and flexibility.

The Unit has achieved a technologically up to date and reliable computing and data analysis service for the School. We aim to maintain and improve information services and techniques where ever possible into the future.

COMPUTING

The Menzies computing requirement has grown considerably due to demand and wider use of computing within the many facets of the School in administration, research and analysis. This has led to the need for more computing resources, flexibility and a good sound infrastructure. The move into the new Combined Health Building has allowed us to provide an infrastructure that is able to grow and change with the School's many directions.

The School has always produced high quality visual aids, posters, videos, CD-ROMs and has on many occasions been awarded for its excellence. The School is increasing its use of multimedia to disseminate information on video, CDROM and over the Internet. The School has recently purchased a digital video camera and editing suite to aid in the production of high quality videos for distribution and broadcasting of information and results produced from projects. Video is a great medium for relaying information back to the Aboriginal community, being visually and aurally oriented, and makes it easy to dub different languages over the same footage without costly translation, unlike textual-based media.

More and more laboratory-based equipment is becoming computer oriented for data collection and analysis with packages such as GelDoc. However many of these areas require large amounts of storage to hold the data and a great deal of memory to analyse the data collected.

The School has relied on having a computer connection to the wider academic and research community from early in its establishment. This was initially to gain access to information and facilities we could not afford to replicate internally, but has expanded to become a main source of communication and dissemination of information from the

School. We have upgraded our link to the Internet in Darwin from a Datel service to ISDN service and now to a 2Mbps Radio link with ISDN backup. Alice Springs have migrated from a dialup link to connection to the NT Government WAN link to Darwin.

The Unit is continually reviewing information procedures used within the School and looking for more effective and efficient means to manage the information around the School.

BIOSTATISTICS

The Biostatistics sub-unit has continued to provide statistical support to the staff and students of Menzies. This support typically takes several forms, including: advice on experimental design; data management; data analysis; modelling; and statistical advice in general.

The main statistical software package used to undertake this support is Stata. Other packages in use at Menzies include: Epi Info (free, easy to use data management and analysis software); Epimod (Epidemiological modelling software developed "in-house"); SPlus (a high level, object-oriented programming language and data analysis package); and numerous other specialty programs.

Recently we conducted a review of packages used by the School for basic statistical and epidemiological methods. The School uses many packages and is making an effort to consolidate these without inconveniencing staff and students with re-training.

Currently we are investigating the use of Markov Chain Monte Carlo simulation techniques to undertake Bayesian analysis of biological data collected by the School. This will allow us to estimate large numbers of parameters (typically) from quite complex models, given modest sample sizes. A Windows-based software package, winBUGS (MRC Biostatistics unit, Cambridge, UK.), is currently being evaluated for such purposes.

SIGNIFICANT COLLABORATIONS

The Unit maintains close collaborations with Northern Territory University (NTU), Northern Territory Clinical School (NTCS), the NT Government Department of Communications and Advance Technologies (DCAT, formerly NCOM), and Territory Health Services (THS).

The Unit is a member of the Northern Territory Regional Network Organisation (NTRNO) as part of the Australian Academic Research Network (AARNet) run by the Australian Vice Chancellors Committee (AVCC). Other members of the NTRNO are NTU, CSIRO, NARU and NTCS.

Laboratory Services

Sue Hutton

The aim of Laboratory Services is to provide a congenial, efficient and safe working environment for the laboratory-based staff and to remain within budget limits each financial year without jeopardising any of the funded research projects.

Over the past five years management of the Menzies laboratory facility has changed from a part time Purchasing Officer position with one support officer to that of a full time Laboratory Manager with two part time Laboratory Support Officers. Increased responsibilities in the management area and then the move to a larger facility in Building 58 in late 1996 justify the upgradings. We farewelled Bee Fong Gunn in November 1994, when she moved to New York with her family. Bee Fong was our Laboratory Purchasing Officer and had been with the School since 1988. Numbers of people doing “bench work” have ranged from 19 to 25 in the laboratories at any one time in the last five years and this year we have been working on 30 funded projects.

PURCHASING

Fast tracking of the purchasing process developed in 1995 has proved extremely beneficial for both laboratory-based researchers, PhD students and the accounts officer. Any perishable item in stock at suppliers interstate is delivered within 24 hours and larger bulk orders or equipment that are road transported are in Darwin in four days. Standing orders for bulk consumables are negotiated annually and price increases have been minimal or remained static since 1995. The cost of annual servicing of biosafety cabinets, microscopes and centrifuges has been minimised by implementation of a scheme whereby the service engineers have been introduced to the NTU and government department laboratory managers. All servicing is performed during the one trip to the Territory, thus the cost of accommodation and airfares is shared. Stock control is semi automated and all assets, suppliers and catalogues are entered onto dedicated databases.

SAFETY

Laboratory safety is of the utmost importance and mandatory new staff orientations have continued since introduction in 1996. An efficient accident reporting and email system ensures that all laboratory staff are kept up to date on all safety issues and the procedures in place to minimise the risk of the same accident re-occurring. Since 1995 we have averaged less than one accident per year. The Laboratory Manager chairs a laboratory safety meeting each month and all issues presented at those meetings are actioned appropriately. Policies including,

- Emergency Evacuation Procedures
- Cyclone Procedures
- Visitors to the Menzies Laboratory
- Delivery of Biological Specimens to the Menzies Laboratory
- Permission to Use Staff Baseline Blood Collections
- Procedures for Use of PC3, PCR and Radiation Rooms

- Sign-off List for all New Employees including Code of Ethics, OHS issues (draft)
- Permission to Access Archival Databases and Stored Samples (draft)
- Work Experience Students Program (draft)
- Correct Collection, Transportation of Specimens and Disposal of Biological Hazards

have been formulated by the Laboratory Manager and verified by the Director and Business Managers.

LABORATORY TRAINEES

The Laboratory Manager has been responsible for the supervision of Department of Employment, Education and Training (DEET) laboratory trainees. Mark Mayo has recently completed his Associate Diploma in Science at NTU and our latest trainee is Melita McKinnon, employed under the CRC training program. The trainees are taught the importance of sterilisation and disinfection of apparatus, how to make media under sterile conditions and the correct procedures for disposal of biological waste. They are then rotated through the laboratories to gain experience in a variety of procedures. This year Grace Perez became the third Transport and Works trainee to work in our microbiology unit. Grace was preceded by Tania Shelby-James who now works at the Flinders Medical Centre in Adelaide and Celina McKean who ventured overseas after her time with us. Tania's dedication and persistence "at the bench" and her pre-planning skills are sorely missed, but Grace is certainly holding the fort since Tania's farewell.

COMBINED HEALTH BUILDING

After spending considerable time since May 1995 on partnering, supervising and consultation with School staff, government agencies, architects, mechanical engineers and local contractors the Laboratory Manager was able to supervise the move from Buildings 4 and 13. The move took less than one week in early November and was an extremely smooth and efficient procedure. One of the highlights was the disruption-free continuation of benchwork over the relocation period. The challenge of managing defects until the end of the defect liability period in August 1997 coupled with the only major design defect – the lack of screening for direct sun exposure on all perimeter rooms, plus the replacement of external defective Robertson wall panels have all contributed to an increased workload for the Laboratory Manager. The new laboratory complex is certainly a significant upgrade on our previous premises and is the envy of all our contemporaries.

FUTURE DIRECTIONS

To maintain a safe, efficient and friendly workplace environment for all laboratory-based staff and students. To optimise energy efficient and resourceful use of the new laboratory facility being mindful of the Federal Governments waste minimisation policy for Australian industry and research institutions. To operate the laboratory facility in such a way as to not jeopardise "good science", nor waste the hard-earned and annually more competitive funding required for health research. To maintain the friendships forged with Engineering Services, Stores, Pharmacy, Laundry and Pathology sections at RDH, as well as various suppliers. To fully computerise ordering, stock control, assets, archived documents and stored specimens possibly using a barcode system. To maintain an international reputation as a recognised first class research facility on the leading edge of medical research by providing effective, efficient management and laboratory support conducive to successful outcomes.

Aboriginal Policy and Health Education Unit

Mai Katona

There have been Aboriginal staff employed on contract basis since the late '80s. The specific role has been to : liaise with communities; discuss research priorities with research staff and communities; explain Aboriginal cultural guidelines to researchers; explain projects to community leaders and potential research subjects; to seek consent; and to provide feedback of research results to the community. The Unit has evolved somewhat in the past decade and increasingly the staff are now applying for research grants as principal investigators. This has signalled the beginning of an important transition for the Unit.

Previously the Unit has undergone many changes and there have been obvious obstacles to implementing recommendations and the aims and objectives of the School. One such example was the Baume report.

The Baume report, commissioned by Menzies in 1991, provided 57 recommendations under headings of "recommendations of principle", "must do recommendations", "should do recommendations" and "could do recommendations". Clearly Menzies had difficulties because the 1990-91 Annual Report on page 24 stated ..

Baume Report [commissioned by the Menzies School] ... The School has shown leadership, nationally, in developing these mechanisms for working with Aboriginal people; nevertheless; the School has had a continuing problem in identifying the funds to resource such projects, which are very labour intensive, because of the need to involve Aboriginal people and to consult fully with them during planning, implementation and feedback of results. As there is also a shortage of trained people, the School has also encouraged as many Aboriginal people as it could to work with the School to develop their skills in health research, evaluation and health development. The School has supported its Aboriginal staff to attend relevant courses (eg. Batchelor College and Northern Territory University).

Despite the problems highlighted with funding, and the shortage of trained people, Menzies is managing to implement an educational program which will, in part, begin to achieve its objectives.

Menzies is towards developing the following three programs.

1. CULTURAL AWARENESS PROGRAMS

This program is developing both European AND Aboriginal cultural awareness programs, which creates a more genuine "cross" cultural program. In the past there has only been mono cultural awareness (about Aboriginal culture). We cannot work successfully if we do not know about each others cultural values, perception and socialisation processes for example. The way in which the term "cross cultural" has been used is clearly a misnomer.

The cultural awareness program will be organised for both European and Aboriginal people which should better assist both groups to work more productively.

2. CAREER STRATEGY

The Career Strategy is in a draft stage and will be widely circulated for comment and input. There are two segments within this strategy. The first is about Menzies accommodating students, trainees and cadetship holders as a host organisation in areas of educational support and work experience. After the individuals have completed their education and training with Menzies, they will have gained sufficient marketable skills to gain employment.

The second segment concerns employment strategy, specifically for those who will have long term employment at Menzies.

The career strategy includes three sub-sections which complement the employment and education direction.

- a. The first sub-section is about Menzies assisting Indigenous secondary school students by conducting a homework centre for maths and science subjects in conjunction with Dripstone High School. It is apparent that Indigenous students require educational support to encourage them to become involved in the health science field. The homework centre will be operational from 2nd Semester 1998.
- b. The second sub-section concerns Menzies being the host organisation for trainees. This year the CRC has funded the trainee scheme, for which Menzies is the host organisation. It is anticipated that trainees will remain within the School for three years and, every third year, Menzies will be host to a new group of trainees. Part of the training agreement is that the individual undertakes tertiary studies.
- c. The third sub-section involves cadetships. The Northern Territory Government, in conjunction with institutions, departments and other organisations, awards scholarships which provide financial assistance for individuals studying at tertiary Institutions. Menzies is currently having discussions with Northern Territory Government representatives regarding the possibility of providing cadetships for Indigenous students to gain tertiary qualifications.

3. RESEARCH

The Aboriginal Policy and Health Education Unit is seeking to develop and implement the following concepts for researchers :

1. Researchers who are working through the Menzies School of Health Research should be informed sufficiently to comprehend the contextual perception of Aborigines in the areas of health research, health development and health evaluation.
2. Researchers should contact Indigenous communities and organisations to obtain information concerning research priorities, planning, ethics, implementation of research, ownership of information and authorship.
3. Researchers should provide framework for joint research proposals with Indigenous communities and organisations.

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4. That the Aboriginal Unit in Menzies or the community members involved in the project will provide feedback of research results. The community involved will also be encouraged to prioritise its actions in relation to the findings and to implement these actions in conjunction with the various service providers.
 5. That all projects being undertaken through Menzies be discussed with the Head of the Aboriginal Unit.
 6. That the communities be encouraged to assess and organise their own priorities in addition to those organised externally.

The following itemised objectives will be implemented over time.

Broad Objectives - Menzies School of Health Research

To :

- Encourage Aboriginal communities to work collaboratively with Researchers on various projects.
- Encourage and assist Aboriginal communities to provide feedback to the various service providers regarding the recommendations of projects being undertaken in their communities.
- Conduct bi-cultural workshops for internal and external staff and other people involved in research in the Indigenous communities.
- Encourage Aboriginal communities to prioritise their own health research.

Specific Objectives - Aboriginal Policy and Health Education Unit

The specific objectives of the Aboriginal Policy and Health Education Unit are to develop, implement and undertake the following :

- skills audit of Unit Staff;
- European cultural awareness program;
- career strategy;
- gain discrete funding for the Unit;
- establish an Education Centre.

PROJECTS

Staff from the Aboriginal Unit are continuing to provide important and valuable links between Menzies and various Aboriginal communities in the top end of the Northern Territory. Staff are also providing feedback to local, national and international communities.

Following is a brief summary of the various projects which members of the Aboriginal Unit are involved in.

Rethinking Compliance

Geoffrey Angeles is working on this CRC-funded project with Dr Kim Humphries of Territory Health Services. The project is aimed at critically exploring issues of

compliance/non-compliance within the context of Indigenous health in the Northern Territory.

Rheumatic Fever Prevention

Loyla Leysley is the trainee assistant researcher in this project. Rheumatic fever prophylaxis is still problematic in many Aboriginal communities. The objectives of the project are to :

- Develop and evaluate strategies to improve adherence with rheumatic fever prophylaxis;
- Reduce the incidence of primary and secondary attacks of rheumatic fever.
- Develop and evaluate strategies to improve understanding of rheumatic fever; and
- Develop and evaluate new health promotional strategies which will be useful for future public health campaigns in Aboriginal communities.

STD Prevention

Norma Bengler is the research assistant in this project being undertaken by Dr Steven Skov. The prevalence of STDs among rural/remote communities in Northern Australia is extremely high. This project aims to determine the best way of reducing STD prevalence in these areas and the cost effectiveness of such programs.

Kava, Alcohol and Their Effects

Peter Thomsen is the assistant researcher. This project aims to provide objective information to Aboriginal communities and individuals, government legislators and policy makers, clinicians and other health workers on some key questions which will enable them to make informed decisions regarding the effects of heavy kava use, particularly when combined with heavy alcohol use.

Otitis media - Randomised Clinical Trials

Harold Koops is the assistant researcher on this project being undertaken by the Ear Health and Education Unit. This project aims to improve the awareness of health staff, mothers and community leaders of the need for early diagnosis and intervention to prevent early onset otitis media from developing into chronic suppurative otitis media that lasts throughout childhood.

Indigenous Health and Education - Exploring the Links

Mai Katona will work as co-researcher with Anne Lowell on this CRC-funded project which will utilise participatory action research strategies to explore the connections between health and education in remote and urban Aboriginal communities in the Northern Territory.

Laboratory Work

Mark Mayo, Louise Martin and Melita McKinnon are employed in the School's laboratory. Mark is involved in the malaria studies being undertaken by the Molecular Parasitology Unit, while Louise is undertaking her BSc(Hons) on investigations into the variation in surface molecules of *Haemophilus influenzae* with the Molecular Parasitology and Ear Health & Education Units. Their work is discussed within the relevant Unit reports. Melita commenced work early in 1998 under the supervision of Laboratory Manager, Sue Hutton. Melita is a CRC trainee with NT Training and will rotate through

the different Units in the laboratory to acquire technical skills in such disciplines as microbiology, molecular parasitology and molecular genetics.



Central Australian Unit

Komla Tsey

This Unit aims to undertake relevant research and development to improve the health of people in Central Australia and beyond. More specifically, we aim to research and disseminate health and other information that will assist the capacity of communities, service providers and policy-makers to address the unacceptable health inequalities between the region's indigenous and non-indigenous populations. The focus of our work continues to be health program evaluation, broadly defined to include needs analysis; program planning and monitoring; policy analysis; service reviews; cost analysis; as well as outcome and impact assessments. The research, consultancies and other activities are characterised by being applied research which has arisen directly from needs identified by service providers. More recently, through our involvement in the CRC for Aboriginal and Tropical Health, we are beginning to diversify our research and development efforts into the area of indigenous education. This is largely the result of a growing recognition of the close correlation between formal education and health status and the need to develop appropriate strategies to address indigenous education disadvantage. Staff of the Unit continue to make significant contributions to the School's Master of Public Health coursework teaching and research student supervision (See under public health training). At an informal level, we continue to provide important research-related advice and other support to organisations and communities throughout the region. All of these have meant a phenomenal increase in the volume of work undertaken within the Unit since the last Quinquennial Review.

ADMINISTRATIVE AND OTHER SUPPORT FACILITIES

Since the last review it has been necessary to expand the capacity of the Unit in terms of its administrative capabilities, space and facilities in order to meet the demands placed on it by the increased activity over the past five years.

At the time of the last review, the Unit was operating with a staff of five out of two small rooms in what was then the NT Department of Health & Community Services Rural District building, with only one desktop PC and a printer. In July 1993 there was a move to a larger, open plan office in the ADRES (Alcohol and Drug Resource and Education Service) building next door. During 1993/94 computer facilities were upgraded, and linked to the MSHR Darwin computer network, providing access to e-mail and other remote electronic services via modem.

During 1995/96 the Unit expanded considerably, staff levels more than doubled from 5 to 12. Dr Komla Tsey took over from Dr David Scrimgeour as Head of Unit in January

1996. In June, under an agreement with Territory Health Services, new premises were leased to the School to house the Central Australian Unit. The “old health promotions building”, as it is commonly known, is a premises for the Unit which provides sufficient space for an optimum staff level of 15. It provides the Unit with its “own” building, resulting in stability, visibility and a clear indication of its independence from THS. As a result of the move it was necessary to purchase equipment such as a photocopier and fax machine, and the phone and computer systems were upgraded and linked to the NT Government communications network. The result of this is speedier and more effective communication generally, especially with MSHR in Darwin.

The Unit has been strengthened administratively during the past five years. At the time of the last review, administrative support was provided by a part time secretary. In March 96, as part of the MSHR five year strategic plan, the Unit identified an urgent need for a full time administrator. An Office Manager position was created and filled, in August 96, by Jackie Parkinson, who transferred from the position of Accounts Officer in Darwin. The presence of an Office Manager has assisted in strengthening the Unit as well as providing a solid administrative structure. The Unit has been able to become more autonomous financially and administratively. Research staff are able to carry out their work without the added burden of the day to day logistics of running the Unit, and liaison between the Unit and administrative staff in Darwin has improved. Cathy Hampton who joined the unit in 1995 continues to provide valuable administrative support on a half time basis along with her duties in the research area.

Other administrative objectives identified in the 5 year strategic plan have also been met as a result of the appointment of the Office Manager. Part of the administrative staff role is that of computer support, and both Jackie’s and Cathy’s computer skills have developed through experience in this area in the past two years. Jackie’s accounting capabilities enable the preparation of financial reports & budgets on site, a valuable assistance to project managers both in terms of financial management of current projects, and in the preparation of new project submissions. Procedures for local purchasing and other administrative arrangements have been put in place, complying with overall School requirements. An orientation handbook has been developed so that new staff are familiar with School procedures and policies.

In addition both Jackie and Cathy have developed skills (largely self taught) in the use of computer graphics packages, enabling visual aids materials and illustrations for publications to be prepared within the Unit. In particular, these skills have been utilised in the Review of Northern Territory Government Remote Health Services report. The library cataloguing system has also been updated and the Unit’s books and other publications are now referenced in the School’s main database.

Both members of administrative staff are currently undertaking study directly relevant to their work at MSHR which will greatly enhance their professional development. Jackie commenced a Bachelor of Business Degree majoring in accounting through NTU earlier this year. Cathy is into her second year of a 4 year Bachelor of Health Sciences Degree majoring in community development and indigenous health, through the University of Sydney. The Unit is fortunate to have a flexible casual administrative assistant, Linda Tate, to assist during study times.

At the time of writing the unit is looking forward to an upgrade of its computer systems. Lack of hard drive space is presenting a problem at present and there is no backup system. Additional software is also required, and the network links to Darwin need to be

adapted in order to run windows-based software directly from the servers. This upgrade is planned to take place over the next month or so.

PROJECTS COMPLETED SINCE THE LAST REVIEW

Adult Health Surveys in 3 Aboriginal Communities in Central Australia

Dr Robyn McDermott undertook this collaborative study with Deakin University. The study commenced in 1994 and aimed to determine the progression - or otherwise - of cardiovascular, renal disease and diabetes in a cohort of Aboriginal adults who were screened some seven years previously. Screening was also offered to other volunteers. In all, a total of nearly 900 adults were screened. The results of the study as reported in the 1994/95 Annual Report (pp57-58) indicate, among other things, that in addition to diabetes and hypertension, there was a large reservoir of (currently asymptomatic) renal disease in the three communities, the cause of which was not clear. This situation, the study concluded, was likely to result in a greatly increased demand for haemodialysis in the next five years, with its consequent very high social and health care costs to the region.

Central Australian Aboriginal Alcohol Program Unit (CAAAPU) Evaluation

Dr Tim Rowse and Ms Kerrie Miller completed the final evaluation of the CAAAPU's three year *Grog Action Plan* in 1994. The evaluation, funded by Australian Brewers' Foundation, found that CAAAPU's first three years were spent establishing residential treatment which the many clients of the program attested to as having beneficial effects on their lives. Unfortunately, CAAAPU had its funding drastically reduced so that residential treatment is no longer available. This study was reported in MSHR Occasional Paper 1/95 [190].

Health Care Expenditure in NT Remote Health Services

This review was undertaken by Ilan Warchivker in 1994/95, at the request of the NT Department of Health and Community Services. The prime aims were 1. to identify and compare health care expenditure per capita in the remote health services and 2. to outline the distribution of resources within each health centre for the type of services it provided. Importantly, the study developed a consistent method of analysing financial flows to remote health services in the NT.

Results were obtained from three areas of the NT (Alice Springs, Darwin and Katherine). An analysis of variation in clinical expenditure per capita identified large variations in health expenditure per capita amongst communities in the three regions. Large variations were identified in the different categories of health care. Generally, small variations were found in the expenditure on doctors' services, and large variations were found in the other expenditure categories. Similarly large variations in grant allocations were identified [266].

Some questions regarding the delivery of health care services in the remote regions of the NT emerged from the study. Firstly, are the current levels of funding health services in the NT sufficient given the health status of the Aboriginal population in the region? Secondly, what are the implications of the variations in clinical expenditure per capita on equity in health care delivery and efficiency of the services delivered? Thirdly, is the mix of services available to the communities providing the best value for money given

population needs, the long distance from hospitals, scattered population, low income levels, lack of healthy food, etc.

Community Involvement in Health Services for Indigenous Peoples

In 1994 Dr David Scrimgeour was granted an NHMRC Public Health Travelling Fellowship to investigate community involvement in health services for indigenous peoples of Canada, Norway and New Zealand. The report of the travelling fellowship found the situations in Canada and New Zealand to be particularly relevant to the Australian Aboriginal health care policy. A major obstacle to the provision of high-quality health services to Australian Aboriginal people continues to be the fact that neither the Commonwealth government, nor the State and Territory governments, accept ultimate responsibility for the funding of Aboriginal health care. David's findings are reported in MSHR Occasional Paper 2/95 [194].

Optional Standards of Care for Frail Aged Aboriginal People

Commenced in 1994, this RHSET-funded project aimed to raise awareness among health care providers in Central Australia about the need to ensure that the rights of frail aged Aboriginal people were respected with regards to their care options. The rationale was to prevent unnecessary nursing home admissions particularly for remote area people. The collaborative project between Central Australian Aboriginal Congress, Central Australian Advocacy Service and MSHR resulted in the development of a 3-hour training course for health professionals, particularly remote area nurses.

An evaluation of the course, carried out in 1995 by Komla Tsey and Alison Lucas, indicated that health professionals with relatively little experience in remote Aboriginal health found the course very useful, whereas the more experienced staff were less enthusiastic about the course, suggesting that the training manual may be more suitable as an orientation tool for new employees [263]. Responsibility for future revisions to the manual has since been transferred to the newly established Central Australian Rural Health Training Unit (CARHTU) in Alice Springs.

Community Control of Aboriginal Health Services in the Northern Territory

In 1996 THS contracted Dr David Scrimgeour for a report on issues surrounding the community control of health services in the NT. The research involved examination of written material and interviews with various people involved in health service delivery. The historical development of Aboriginal community controlled health services was outlined, and the responses of government to this significant indigenous social movement discussed. The study highlights the benefits and problems of community-controlled health services, particularly in remote areas. The report contains specific recommendations for future policy directions for THS in supporting Aboriginal self-determination in health care. [195, 257, 310]

Evaluation of Diabetes Control Activities in Central Australia

This project, undertaken by David Scrimgeour, Alison Lucas and Tim Rowse, was funded by NHMRC. Qualitative research into the perceptions of both providers of health care to Aboriginal people with diabetes in Central Australia, and the recipients of this care, regarding problems and issues surrounding the management of diabetes was undertaken. Interviews with Aboriginal people demonstrated that there is a widespread understanding of diabetes as one of a group of "whiteman's" diseases which was

introduced into Aboriginal society as a result of changes brought about by European colonisation. Consequently, diabetes is seen as a disease which does not respond to traditional treatments, but which falls into the domain of the western medical health care system. Health care providers also tended to view diabetes in its historical and social context, but often this was the basis of a sense of futility regarding the possibility of providing appropriate medical care for Aboriginal people with diabetes.

It was suggested that, whereas there is clearly a need for improvements in the social and economic conditions of Aboriginal communities, Aboriginal people with diabetes need proper medical care and that, although the perceptions of Aboriginal people regarding diabetes is conducive to a negotiated compromise between different, though significantly overlapping goals between practitioner and patient, it is sometimes the attitude of health care providers which results in less than optimal care. Findings are reported in MSHR Occasional Paper 3/97 [311].

Evaluation of Tri-State STD/HIV Project

This study was undertaken in 1996 by David Scrimgeour and Komla Tsey and funded by the AIDS Education Branch of the Commonwealth Department of Human Services and Health (now Health and Family Services). The Tri-State Project itself was a 2-year cost-sharing pilot initiative between the Health Departments of the Northern Territory, South Australia and Western Australia, as well as the Commonwealth. It aimed to develop a coordinated approach to Sexually Transmitted Diseases (STD) service delivery in the cross-border regions of Central Australia. The rationale was to overcome a lack of coordination and uniformity to STD management, which was perceived to be a barrier to effective service delivery across the three health jurisdictions. Using a combination of qualitative and quantitative methodologies, the results of the evaluation indicate that the Tri-State has made impressive progress towards improving STD control in Central Australia (which should have the effect of reducing the potential for rapid spread of HIV in the area). In the area of clinical management of STDs, the Tri-State was involved in, for example, active case-finding programmes for gonorrhoea and Chlamydia, using urine PCR tests, which demonstrated the high prevalence of these diseases in the area, and also demonstrated that urine PCR testing for gonorrhoea and Chlamydia is an acceptable alternative to genital swabs for diagnosis of these diseases. In the area of education too, a methodology for interactive community education was developed, and workshops were held for people working in health services and other organisations to develop skills in community education techniques. Despite these and other significant gains, the Tri-State was criticised for its approach. Generally the criticisms have reflected structural concerns about the role of regional health programmes vis-a-vis community based primary health care agencies. The report (MSHR Occasional Paper 1/97, [312]) includes specific recommendations to overcome the structural concerns. Overall, the contribution of the Tri-State project towards better control of STD/HIV in Central Australia suggests the need to examine more closely the potential for applying the 'cross-border' concept to other public health programmes in the region.

Review of Northern Territory Government Remote Health Services in Central Australia

This review, funded by Territory Health Services and the Commonwealth RHSET program, was undertaken by John Wakerman, Marlene Bennett Nungarai, Virginia Healy and Ilan Warchivker. Working with an Aboriginal steering committee, the multidisciplinary Menzies team examined :

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1. issues related to increasing community control of government health services, particularly how to better inform communities of service issues;
 2. different models of service delivery in order to increase efficiency and provide better access, particularly to small, remote communities;
 3. health expenditure by community and methods of more equitable distribution of health resources; and
 4. implementation strategies.

Methodology included extensive community consultation, the development of explanatory tools to impart health service information to communities and a significant quantitative component related to detailed expenditure analysis.

We developed the following :

1. a definition of basic remote area Primary Health Care functions;
2. decentralised, integrated models of service delivery;
3. an algorithm for resource allocation to remote communities in the region; and
4. criteria for prioritising resource allocation. Costings indicated a significant resource gap between current resources and those needed to provide access to basic services in remote areas.

Currently the report [323] rests with Territory Health Services for implementation.

Ambulatory Care Project (Part C) : An Analysis of Models of Remote Area Health Service Delivery in the Northern Territory

This project, undertaken by John Wakerman, Ilan Warchivker, John Tregenza and John Grundy, was funded by Territory Health Services as part of a larger Ambulatory Care program. The objectives of the project were (1) to improve the overall effectiveness and efficiency of ambulatory care services in remote parts of NT by systematically evaluating existing service models and considering alternative models and (2) to describe four different existing models of primary health care (PHC) to remote Aboriginal communities in the NT and evaluate their effectiveness.

A combination of qualitative and quantitative methodologies were employed. The four remote health services involved in the Ambulatory Care Project (Part C) were identified on the basis of their diversity of management and population structures. The four services demonstrate a range of funding sources, differing levels of dispersion of the population and different models of health service delivery and management.

In brief, the types of priority health issues identified for each community were as follows :

- | | |
|-------------|---|
| Community 1 | Petrol sniffing, child neglect, inadequate housing and overcrowding. Of medical priorities, diabetes is the highest, and ranked at number 7 overall. |
| Community 2 | Health hardware (including power), rubbish collection, housing/overcrowding. The highest ranked "medical" issues were aged care, ranked 6, and disabled/palliative care, ranked 8. |
| Community 3 | Dog health, health hardware, insufficient Aboriginal Health Workers, especially male AHWs, issues to do with wages and withholding of wages, housing/overcrowding, neglected children. Eye health was ranked at number 8. |
| Community 4 | Aged care, health hardware, wages and income. Gastroenteritis/diarrhoea was ranked at number 5. |

Hospital separations were analysed. The striking features of this analysis are :

1. the high number of admissions in the 0-5 age group. These rates are between 5 and 10 times Australian rates. A large proportion of these admissions are in diagnostic related groups to gut and chest infections. Congruently, environmental issues were commonly identified by communities as health priorities. Environmental health expenditure at community level is relatively low.
2. Separation rates in adults over 50 remain fairly constant. The pattern for Australia overall is a distinct rise in hospitalisation rates for older age groups. This difference is surprising considering the high morbidity and mortality rates observed in adult Aboriginals.
3. The low proportion of healthy neonates born at Alice Springs Hospital.

Recommendations in the current Draft Report are in the following areas :

- Greater emphasis on preventive and health promotion activities initiated, planned and implemented by communities.
- Structures for enhanced community participation, *eg.*
 - proposed health committee in one community;
 - service agreements between service providers, funders and consumers.
- Capacity building and training for Aboriginal and non-Aboriginal staff. Questions which need to be addressed include : What is evaluation? How do you plan? What is the role of the health committee? Why have local health policies and how do you formulate policy? How do you assess health information?
- Systems for needs assessment, planning and evaluation in order to re-orient services.
- Develop mechanisms for intersectoral action.

CURRENT PROJECTS

An Evaluability Assessment of Central Australian Mental Health Services

Between May 1996 and June 1997, Komla Tsey, David Scrimgeour and Cassandra McNaught carried out an evaluability assessment as a first step in a two and a half year NHMRC (Health and Family Services Research and Development Grant) funded *Central Australian Mental Health Service Evaluation* project. Lack of stakeholder agreement on the types of services that should be available to people in the region and how they should be delivered; disagreements over the boundaries of the Mental Health Service (MHS) *vis-a-vis* other agencies, especially Aboriginal community organisations; as well as a lack of information concerning the levels and mix of resources required for the MHS to provide its share of services in a culturally acceptable form, among others, emerge as the main barriers to effective mental health service planning and evaluation in Central Australia. The evaluability assessment report was released as MSHR Occasional Paper 1/98 [392].

The substantive evaluation which is currently being implemented by Ms Ann O’Kane, as Senior Research Officer, include :

- identification of a list of “prescribed mental health services” which should be accessible to all (Central) Australian residents;
- through a process of consensus, determining the service boundaries of the MHS (*ie.* the range of “prescribed” services that the MHS should be providing including the dollar costs of resources required to provide such services in a culturally acceptable manner);
- assisting each support program area of the MHS to develop a system of ongoing evaluation within an overall context of effective planning;

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- negotiating and monitoring a set of preliminary recommendations arising from the evaluability assessment.

Evaluation of Central Australian Aboriginal Congress Community Health Program

The Community Health Program (CHP) is the 'outreach' branch of Congress through which the organisation seeks to extend its services beyond the clinic to the wider Aboriginal Community in and around Alice Springs. CHP is made up of several discrete programs including an outstations mobile service; immunisation; nutrition; school health program; and aged care. Funded by Department of Health and Family Services, Divisions and Projects, this evaluation aims, among others, to assist Aboriginal health workers and other CHP staff and management in determining a) the extent to which the original aims and objectives of the program are being achieved and b) what changes, if any, are needed to make the program more effective. A draft evaluation report including detailed recommendations formed the subject of a workshop with CHP staff and management in 1997. The main recommendations are now being implemented and a final report will be produced later in the year. One of the useful lessons from this evaluation is its collaborative approach : Brenda Austin, a permanent staff of congress was seconded to work with Menzies staff (Komla Tsey and David Scrimgeour) on the evaluation. We found this "insider" and "outsider" collaboration to be a very useful approach to service evaluation.

Evaluation of the "Wise Use of Medicine" Project

The "Wise Use of Medicine" project is a collaborative health promotion initiative by the Tangentyere Council and Central Australian Aboriginal Congress. Funded by the Commonwealth's Council on Ageing, and undertaken by Cathy Hampton, the project aims to assist Aboriginal health and aged care workers in enhancing drug compliance among older Aboriginal people. The objective is to produce educational resources including posters and videos to address issues relating to management of medicines including safe storage, remembering to take multiple medicines, preparing daily doses of medicines, and techniques to enhance doctor/patient communication. The evaluation will monitor and assess the impact of the project.

Developing a Preventive Approach to Nutrition Problems in a Remote Community

This is a collaborative RHSET-funded project with Pintubi Homelands Health Service, a remote Aboriginal health service, to facilitate the development of an interagency nutrition program in a remote community in Central Australia. The project, commenced in May 1998, is being undertaken by John Wakerman and Ilan Warchivker from MSHR. It includes monitoring and evaluation, in order to support consumers' efforts to improve child health and prevent hospital admissions. The project commenced in May 1998.

The project involves consumers and a multidisciplinary health team: Aboriginal Health workers, nurses, a doctor, nutritionist, women's centre co-ordinator and community nutrition workers. This community-initiated program may provide a model for other communities to help re-orient services to preventive and health promotion activities. Calculation and documentation of demonstrated savings in hospital admissions would support ongoing funding of this initiative and establish other community-based interventions.

The objectives of the project are :

- To develop a best practice, community-based nutrition program with an emphasis on education of consumers and staff.
- To decrease childhood nutrition-related hospital admissions from one remote community.

Improving Management in a Cross Cultural Context

MSHR has recently received funding from RHSET to undertake this collaborative project with the Indigenous Primary Health Care Program, University of Queensland. John Wakerman and Peter Hill will analyse, document and disseminate information relating to management in an indigenous context, in order to increase the number of Aboriginal and Torres Strait Islander managers and improve acceptability of health services for indigenous people.

Over the past two decades, larger Aboriginal organisations have created an environment that has produced an echelon of senior Aboriginal managers. The recent Review of NT Government Remote Health Services in Central Australia recommends a number of Area Managers working within multidisciplinary teams. It is predicted that most of these managers will be non-Aboriginal. An identified barrier to improved acceptability of, and thus access to, some remote health services is the lack of indigenous people in senior management positions. There is a challenge for state health authorities and other remote health service providers to refocus management structures and styles to better reflect Aboriginal values and facilitate the process of Aboriginal people taking up more senior management positions in rural and remote communities.

The short term objectives are to : (1) better inform indigenous aspirants to health service management positions about potential options and strategies and (2) to inform and sensitise non-indigenous managers and policy-makers to issues relating to indigenous managers. In the longer term, to help increase the number of indigenous health service managers in rural and remote areas and improve access to for indigenous consumers.

CRC Cross-Cultural Education and Research Program

A recent exciting and challenging development has been our involvement in the CRC for Aboriginal and Tropical Health. As Program Leader, Komla Tsey coordinates the Cross-Cultural Education and Research Program from this Unit. Two full time Research Fellows currently work in the program - Dr Bob Boughton, based in Alice Springs, and Dr Anne Lowell, based in Darwin. We look forward to developing a long-term sustainable collaborative research program to address issues relating to indigenous education and health (See under the School's collaborative activities).

OTHER ACTIVITIES

- Chair Alice Springs Institutional Ethics Committee (Dr D Scrimgeour, currently Dr J Wakerman)
- Member Reference Group OATSIHS National Aboriginal Health Workforce Modelling Project (Dr J Wakerman)
- AusAID consultancies: Team Leader Fiji Health Management Reform Project Design Team (Dr J Wakerman, 1998)
- WHO consultancies: Documentation of Polio Eradication in the Pacific (Dr J Wakerman, 1997)

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- Member National Heart Foundation Rural and Remote Issues Advisory Committee (Dr J Wakerman, 1998)
 - Member of Australasian Faculty of Public Health Medicine Council (Dr J Wakerman, 1998)
 - Setting up the data base for the Tangentyere Social Behaviour Program (I Warchivker)
 - Costings for the Tiwi Island Dialysis Feasibility Study (I Warchivker)
 - Involvement in the Coordinated Care Trials Evaluation (I Warchivker)
 - Developing a projection model for the numbers of patients requiring renal replacement therapy (RRT) in Central Australia (I Warchivker)
 - Editor, *Central Australian Rural Practitioners Association (CARPA) Newsletter* (R McDermott, 1993/94; Komla Tsey, since 1995)
 - Dr Komla Tsey's on-going longitudinal study of traditional healers in Ghana continue to yield positive results. Commenced over six years ago, the study was designed to follow a cohort of traditional healers and generations of their apprentices over a twenty year period to determine, among other things, trends in the transmission of indigenous knowledge systems from one generation to another in an increasingly globalised world [256, 321, 390].

THE FUTURE

As our activities over the past five years have shown, we have been extremely successful in attracting funding to undertake relevant research largely in response to the needs of service providers. This is particularly the case given the size of our 'core' funded staff—two full time equivalent (FTE) academic positions and two FTE administrative support. We wish to build on our strength in attracting funds in support of relevant research and development throughout the region. However, we also need to consider ways of providing security for some of our long serving project funded staff so as to enhance the stability of the Unit. A striking feature of most of our projects in the recent past has been attempts to feed research information back to relevant communities and other stakeholders. This has been a positive development which we need to continue. However, in the next five years, we need to develop strategies to ensure that, as researchers, we have a continuing role in the implementation of the recommendations of research reports. We also need to devote more time and resources to addressing the basic question: to what extent are our research and development efforts impacting on Aboriginal health? Methodologies may need to be developed to empirically show the impact of our research efforts as a way of re-assuring both ourselves and the communities with whom we work. This may be a useful project for the CRC for Aboriginal and Tropical Health to consider.

Clinical Unit

Bart Currie

The emphasis for the Clinical Unit is on collaboration with both local health professionals and experts outside the NT to address health issues important for the region. Studies are targeted at improving prevention and treatment of specific illnesses, usually through a better understanding of the underlying disease processes. Epidemiology, clinical observations and basic laboratory work are all involved.

INFECTIOUS DISEASES

Antibiotic Guidelines and Treatment Protocols

The national Antibiotic Guidelines are revised and published every two years. There continues to be a major input from work done in the Territory. In the 1998/99 edition the remote areas section, written from MSHR, was incorporated into the main chapters, with consequent strengthening of the national applicability of protocols developed in the NT for skin sepsis, scabies, rheumatic fever prophylaxis, trachoma, melioidosis, STDs and malaria. The revision of the CARPA Manual from Central Australia is also informing national and Territory-wide protocols. In addition, the emergence and epidemiology of antibiotic resistance in various organisms and associations with antibiotic use are being studied. Of particular concern are increasing resistance of *Streptococcus pneumoniae* to penicillin and other antibiotics [290], the emergence and spread of community-acquired methicillin resistant *Staphylococcus aureus* in the Northern Territory [244] and Western Australia, and the potential for increasing macrolide (eg. erythromycin) resistance with extensive use of azithromycin [298, 152].

Melioidosis and Pneumonia

Since late 1989 there has been a continuing prospective study of community-acquired pneumonia and melioidosis coordinated by the Clinical Unit. We have now documented over 200 cases of melioidosis, by far the largest study in Australia [16, 19]. Melioidosis is the commonest cause of fatal bacteraemic community-acquired pneumonia in the top end and at Royal Darwin Hospital [24, 46, 86, 154, 155]. In collaboration with hospital laboratory and clinical staff and the NT Centre for Disease Control we have devised improved diagnosis and treatment protocols and education packages for health staff and the public. Although melioidosis remains a devastating infection in certain circumstances, the mortality of those infected has been significantly reduced in the top end. Our clinical study has enabled various collaborative projects on epidemiology and pathogenesis within Menzies and externally [165].

Work continues on improving our understanding of the epidemiology, pathogenesis and best clinical treatment of community-acquired pneumonia and melioidosis. With Dr Anton Janmaat and other veterinary colleagues at NT Dept of Primary Industry and Fisheries, we are looking at the relationship of soil contamination with the melioidosis bacteria, *Burkholderia pseudomallei*, to animal and human melioidosis disease [166]. Dr Jodie Low Choy, a Darwin veterinarian, was awarded the Roy and Marjory Edwards Fellowship for 1997 to look at the epidemiology and clinical feature of melioidosis in

animals in the top end. Melioidosis has a major impact, especially on goats, in the tropics and the public health implications of this included the concern of disease transmission to humans ingesting unpasteurised goats milk. Work at MSHR enabled the NT Dept of Health to implement a pasteurisation support scheme for NT goat farmers. We are assessing the level of environmental contamination with *B. pseudomallei* in a remote community experiencing a concerning high number of melioidosis cases and fatalities. This work is in collaboration with Phil Donohoe, THS Environmental Health Officer for East Arnhem and community health staff. In that and some other remote communities an association between excessive kava consumption and melioidosis is being investigated in collaboration with Health Centre Staff and Dr Paul Spillane. Alan Clough has begun work on an NHMRC funded project assessing the health effects of kava consumption, following on from the preliminary work of Chris Burns (see below).

Analysis of the PCR diagnostic tests for rapid detection of *B. pseudomallei* has been completed following work by Dr Antje Haase and Maree Brennan [352]. While the PCR increases sensitivity of diagnosis, false positive results currently give a clinically unacceptably low specificity. Hence we will for the present be restricting PCR to environmental studies, while relying on the traditional expert culturing and identification skills of the Royal Darwin Hospital Microbiology staff, directed by Dr Gary Lum, for clinical samples.

Mark Mayo, in conjunction with Antje Haase, Dave Kemp and Maree Brennan has developed a neat Pulsed Field Gel Electrophoresis method for typing *B. pseudomallei* isolates for the molecular epidemiology studies of melioidosis. We are using this method to answer questions on relationships between environmental and human isolates (confirming two local "outbreaks" to be clonal and related to isolates from the local environment and in one case suggesting contamination of the unchlorinated community water supply).

Scabies

Protocols of scabies programs for community and hospital use are being refined. The role of oral ivermectin therapy in refractory crusted (Norwegian) scabies is being studied. Failure of ivermectin to give sustained benefit in some cases, despite repeated doses [160, 286], emphasises the need for a community approach to treat contacts who are potential sources of reinfestation and to support hygiene measures and household environmental cleaning. Infectious Diseases Registrars Drs Sarah Huffam and Daniel O'Brien at Royal Darwin Hospital have collated important data on ivermectin therapy in crusted scabies [295, 296, 360].

See also the section in Group A Streptococcal Diseases below and the Molecular Parasitology Unit report on Shelley Walton's PhD study developing molecular typing of scabies mites [324]. NHMRC funding has been obtained to look at the immunological basis of crusted scabies in Aboriginal communities - a devastating illness with high mortality.

GROUP A STREPTOCOCCAL DISEASES

Jonathan Carapetis' PhD involved looking at the epidemiology of group A streptococcal (GAS) diseases in Aboriginal and non-Aboriginal Australians of the Top End, as well as the most comprehensive study of clinical and epidemiological aspects of rheumatic fever and rheumatic heart disease undertaken in Australia [145-147, 338]. He

documented for top end Aboriginal children the highest incidence rates of rheumatic fever published anywhere. In 1996-98 he looked further at practical aspects of preventing and controlling these diseases.

Acute Rheumatic Fever and Rheumatic Heart Disease

The database of all known or suspected cases of ARF and RHD has been maintained, and provides the best available data on incidence of ARF and prevalence of RHD in Aboriginal Australians in the Top End [279, 280, 337]. These figures were presented at the 1996 Lancefield Symposium on Streptococci and Streptococcal Diseases in Paris. At that meeting it became clear that Menzies is one of very few institutions around the world undertaking the combination of field epidemiology and molecular biological research which may help to answer the outstanding questions regarding ARF pathogenesis and control. The database has also helped to identify particular deficiencies in present approaches to controlling ARF and RHD; poor adherence to secondary prophylaxis and inadequate follow-up and provision of clinical services. As a result, Menzies, together with the NT Centre for Disease Control and the NT Division of the National Heart Foundation, successfully applied for Commonwealth Government funding for the establishment of a Control Program for Rheumatic Fever and Rheumatic Heart Disease. This program, based around the establishment of a computerised register of all ARF/RHD patients and a series of educational packages (see below), began in early 1998 and has drawn together many different people involved in education and health provision. The program is now run by Disease Control, using Menzies resources for educational activities and ongoing evaluation. It represents the ideal of moving from applied research to improved service delivery.

We are undertaking an audit of the outcomes of heart valve surgery for RHD, to look at the survival after surgery, the incidence of complications, and whether there are pre-operative predictors of good or poor. In the meantime, new approaches to surgery are being considered, and a number of patients are undergoing heart valve repair, rather than replacement.

Our field and laboratory work has also led to new approaches to primary prevention. Traditional strategies for primary prevention of ARF are based on the seminal studies of GAS epidemiology from the 1940s through the 1970s, largely in the USA. The pioneering studies of the Molecular Genetics Unit in developing rapid, cheap methods for molecular typing of field isolates, has clarified GAS epidemiology in this hyperendemic region, and is helping to show how GAS epidemiology in the Top End is very different from that in industrialised countries [168, 199, 287]. It is clear that the load of infection with numerous distinct strains, at the individual and community level, is enormous. Moreover, the traditional distinction between "skin" and "throat" isolates appears to be blurred. We are challenging the dogma that skin sores have no role in ARF pathogenesis, and are promoting strategies for reducing rates of streptococcal pyoderma as a form of primary ARF prevention (see below) [222]. Primary prophylaxis for streptococcal sore throat remains extremely important, and further work is needed to understand the epidemiology of sore throat and GAS pharyngitis in this region.

Rheumatic Fever Information Package

Geoffrey Angeles and Norma Bengner have been instrumental in publishing two popular educational booklets about rheumatic fever - "*The Rheumatic Fever Story*" [212] and a book for adults, "*Rheumatic Fever : Questions and Answers*" [213]. Subsequently, with Liz Stubbs

and clinical staff, they produced a rheumatic fever video, which was launched in early 1998.

It is pleasing to note that the books are in circulation in a number of communities and are being used by people with rheumatic fever and clinical and hospital staff. We have had reports from some communities that the books and the associated penicillin needle charts have helped to improve the rates of adherence to preventive medication.

The AMP Foundation and the Australian Rotary Health Research Fund provided valuable support for these projects.

Geoffrey Angeles has also been successful in acquiring a RHSET grant to formally evaluate the package in three communities as a pilot program. Part of the evaluation will be to use a workshop strategy to provide Aboriginal Health Workers with information about rheumatic fever, so that they may use the package to educate their own people, in their own way.

Acute Post-Streptococcal Glomerulonephritis

This disease continues to occur sporadically and in epidemics in the Top End. We have documented incidence rates of APSGN among the highest in the world. In conjunction with the Centre for Disease Control, we looked at the response to a recent large outbreak in a number of communities, and evaluated the strategy of delivering benzathine penicillin G injections to all children in affected communities, as a way of halting outbreaks [145]. The resulting protocol recommends that such a strategy does appear to work, but that the target group could be narrowed to children with skin sores and household contacts of APSGN cases.

Streptococcal Pyoderma and Scabies

Together with the Centre for Disease Control, we continued to assist one remote Aboriginal community in controlling their scabies problem [278], using an adaptation of a community scabies control model devised and published by Professor David Taplin at the University of Miami, USA. This program has run for over two years, and resulted in dramatic reductions in scabies rates, and in rates and severity of skin sores. We have assisted the Centre for Disease Control in writing a protocol for other communities to use, and similar programs will hopefully be established around the Top End over the next few years.

Towards a Group A Streptococcal Vaccine

Our ongoing collaboration continues with Professor Michael Good's team at the Queensland Institute of Medical Research. They are narrowing down a small area of the surface M protein of GAS, which is a potential vaccine candidate [118, 119, 253]. We are undertaking field studies in collaboration with Linda Selvey from Queensland Health and Evelyn Brandt from QIMR to look at the immunological responses to this peptide in children and adults in Aboriginal communities [219]. This will help ascertain whether naturally acquired antibodies to the peptide are indeed predictive of protection from GAS colonisation and/or disease sequelae.

Invasive Group A Streptococcal Diseases

With Dr Adrian Walker, Paediatric Registrar at Royal Darwin Hospital, we have undertaken an audit of invasive GAS infection cases over six years at RDH [340]. The results are presently being analysed. Molecular typing of the invasive GAS isolates is currently being undertaken by Megan Hibble of the Molecular Genetics Unit. Megan is attempting to determine whether the risk and severity of infection in this region is similar to elsewhere in Australia and overseas, and whether features of the isolates are representative of those found in the community.

OTHER INFECTIOUS DISEASES

Collaborative projects continue with the NT Centre for Disease Control, colleagues from Royal Darwin Hospital, NT Medical Entomology, under the direction of Peter Whelan, rural communities, NT Dept of Primary Industry and Fisheries and various interstate colleagues [15]. Areas include malaria [18, 26, 101, 128, 129, 158, 226, 285], arboviruses, leprosy [237, 238], hospital infections [28, 32, 74, 89, 170, 171, 362, 376], zoonoses and environmental pathogens [25, 228, 229], sexually transmitted diseases [76, 116, 117] and hepatitis [75, 169].

SUBSTANCE ABUSE

The work from Chris Burns' PhD thesis, completed in late 1996, continues to provide useful objective information in the current debate on petrol sniffing issues, especially in the area of policy recommendations [79-81, 87, 141, 142, 144, 220]. A summary of the recommendations from his thesis are included in the *General Recommendations* box below :

GENERAL RECOMMENDATIONS

HARM-REDUCTION STRATEGIES

Recommendation 1. That, as a medium term strategy in order to reduce mortality and morbidity requiring hospitalisation amongst petrol sniffers, consideration be given to the use of unleaded petrol as a harm-reduction strategy in those communities in which prevention strategies (including Avgas) continue to be unsuccessful.

The following recommendations describe how this could be accomplished.

Recommendation 1.1 That, at a Commonwealth level within the Department of Health and Family Services, there is development of a program and suitable materials to enable affected Aboriginal communities, their organisations and State and Territory Health Departments to be informed about the possible use of unleaded petrol as a harm-reduction strategy;

Recommendation 1.2 That such programs and materials clearly identify the possible benefits and potential for long term toxicity of use of unleaded petrol. This also includes the incorporation of information from research into the possible long term toxicity that may result from chronic inhalation of unleaded petrol (see also suggestions for further research);

continued ...

Recommendation 1.3 That the development of such a program and materials draws heavily upon the knowledge and skills of Aboriginal people resident in those affected communities;

PREVENTION STRATEGIES

Recommendation 2. That the development of a number of coordinated strategy options be considered in the prevention of petrol sniffing.

Although the following recommendations describe how this might be accomplished, there is much to learn from the Petrol Link Up Project in Central Australia (Shaw et al., 1994) which provided a regional focus for affected Aboriginal communities and easily accessible information on a range of prevention strategies. Unfortunately this program ceased in 1994 because of lack of funding. The Petrol Link Up Project could serve as a useful model for implementing these recommendations and the preceding recommendations should they be taken up by Government.

Recommendation 2.1 That, as in Recommendations 1.1 and 1.3 there is development of a program at a Commonwealth level within the Department of Health and Family Services, to resource and inform affected Aboriginal communities on suitable and effective strategies that may be developed to prevent petrol sniffing;

Recommendation 2.2 That the development of such strategies be tailored to meet the unique history, nature and needs of a particular community (see also suggestions for further research). This process should encourage local Aboriginal residents to develop effective strategies which may incorporate elements that have been shown to be successful elsewhere;

Recommendation 2.3 Those communities considering the use of Avgas strategy or those who have only achieved partial success should be encouraged to examine a range of strategy options, particularly employment and skills training strategies;

Recommendation 2.4 That the Commonwealth Government, through its relevant Departments, ensure that affected Aboriginal Communities receive priority in access and funding for employment and skills training programs and other suitable economic benefits such as contracts for housing construction, so that young people on those communities are offered meaningful and productive alternatives to petrol sniffing;

Recommendation 2.5 That relevant Commonwealth, State and Territory authorities examine the further development of suitable family and community based counselling programs for alcohol and other drug use (including petrol sniffing). These programs should be developed on a model suitable for Aboriginal people (see also suggestions for further research);

Recommendation 2.6 That relevant Commonwealth, State and Territory authorities examine the further development of suitable health promotion material relating to petrol sniffing for use in schools and at a community level. Wherever possible such material should incorporate Aboriginal input to make it appealing and effective (see also suggestions for further research);

During 1997 Chris became involved in kava issues in two related areas. Firstly, he assisted Dr Peter d'Abbs in the preparation of an extensive review [327] on the economic, social, cultural and health effects of kava for the NT Parliamentary Committee which developed a Kava Management Act. Secondly, he assisted the Yirrkala Dhanbul

Community Council and the Maningrida Community Council to develop community based strategies to reduce kava consumption. Subsequently Chris was successful in obtaining NHMRC funding for a three year project beginning 1998 to look at the health effects of kava consumption, with Alan Clough employed as the project officer. Preliminary work has shown a large economic burden on families from the million dollar plus black market in purchasing kava.

OTHER SERVICE DELIVERY STUDIES

In 1995/6 Chris undertook the Maningrida Feasibility Study and Health Services Plan [143], making recommendations for improved service delivery and health infrastructure. The study was funded from the Commonwealth and involved extensive consultation with community members and health staff. The findings and recommendations clearly documented the need for increased funding and the complexities of the problems in providing adequate services for remote communities.

In 1995 Grant Mackenzie undertook his BMedSci thesis looking at discharge summaries on patients admitted to Royal Darwin Hospital. He looked particularly at issues of communication between hospital staff and those working in remote Aboriginal communities [183]. Obstacles to efficient and effective communication of quality information were identified and recommendations for improvements made. Parallel initiatives from Territory Health Services had similar findings and subsequent changes to the discharge and discharge summary processes at the hospital have led to substantial improvements.

THE ABORIGINAL BIRTH COHORT STUDY

The detailed study continues of a birth cohort of 686 liveborn singletons born at the Royal Darwin Hospital to mothers self identified as Aboriginal prospectively collected from 1987-1991. This study began with the aim of relating birth outcomes to birth antecedents and later morbidity and mortality [54, 55, 184, 308, 309, 309A].

High risk referrals from adjacent health regions accounted for 116 of the infants but the remaining 570 infants were routine deliveries from the Darwin Health Region. The mean birth weight of the studies infants was 3080 g (standard deviation 606 g), 14% were low birth weight (LBW), 7.4% preterm and 25% had intrauterine growth retardation (IUGR). Of the 70 LBW infants 47% were preterm and 70% were IUGR (**Table 1**).

The prevalence of maternal disease was high, 63% of mothers were in more than one disease group. Over a quarter of mothers had anaemia during pregnancy and one-fifth had urinary tract infection or evidence of genital infection. Fifteen percent of mothers had a body mass index (BMI) below 18.5 kg/m², indicative of moderate malnutrition (**Table 2**).

Table 1. Relationship between LBW, IUGR and preterm birth for 503 Aboriginal infants born at Royal Darwin Hospital, 1987-91 (from Sayers and Powers, 1997)

Classification	Preterm birth	Term birth	Total
With LBW*			
IUGR@	13	36	49
Not IUGR	20	1	21
Not LBW			
IUGR	0	77	77
Not IUGR	4	352	356
Total	37	466	503

* LBW: < 2500g

@: IUGR, < 10th centile of birthweight for sex and gestation

Table 2. Possible explanatory variables for perinatal outcomes of 503 single live births at RDH, 1987-199 (from Sayers and Powers, 1997)

Description of Variable	%	Total
<i>Maternal characteristics</i>		
Age		
<20 years	32.0	503
≥35 years	4.6	503
Underweight (BMI <18.5 kg/m ²)	15.4	357
Overweight (BMI ≥ 25 kg/m ²)	20.4	357
Smokes per day		
up to half a packet of cigarettes	19.8	500
over half a packet	33.8	500
Drinks alcohol	12.7	498
Primipara	34.0	503
Inadequate antenatal care (started after week 16 or <50% recommended visits)	57.3	431
Rural resident	76.1	503
No non-Aboriginal ancestor	76.7	503
<i>Maternal history for this pregnancy</i>		
Anaemia (Haemoglobin < 100 g/l)	26.3	502
Urinary tract infection (positive culture)	19.9	502
Chronic respiratory conditions	3.4	502
Diabetes (gestational or other)	3.4	502
Gestational diabetes	2.6	502
Diabetes (abnormal GTT prior to pregnancy)	0.8	502
Genital diseases	21.7	503
Chlamydia	5.4	502
Syphilis	3.8	502
Gonococcus	2.2	503
Candida	11.1	503
Trichomonas	4.6	503
Other genital infections	2.2	503
Other medical disease	20.9	503
Acute respiratory infection	7.6	502
Heart disease	1.0	502
Hypertension	0.8	502
Hepatitis B	6.0	502
Skin problems	3.4	503
Other medical conditions	5.2	502

Obstetric history

Prolonged rupture of membranes	3.4	502
Pregnancy induced hypertension (DBP \geq 90mm Hg with oedema and proteinuria)	9.0	502
Other obstetric condition	3.6	502
Antepartum haemorrhage	2.0	502
Other obstetric problems	1.8	492

* Percentages do not include missing values.

Note: Variables were coded 1=true and 0=false

Mothers with a BMI < 18.5kg/m² had five times the risk of having a LBW infant and 2.5 times the risk of IUGR. Population attributable risk (PAR) percentages suggested 28% of LBW and 15% of IUGR could be attributed to poor maternal nutrition. Risk percentages for maternal smoking were 18% for LBW and 10% for IUGR. For IUGR, 18% could be attributed to maternal age less than 20 years of age. Risk factors for preterm infants were predominantly obstetric: PAR for pregnancy induced hypertension was 26% and for other obstetric conditions 16%.

Growth and morbidity data measured by hospital admissions and days has been continuously collected on this cohort for the last ten years.

Community Feedback

Results have been published in peer reviewed journals and presented at conferences. Feedback to the Aboriginal community has been through the Aboriginal Health Worker Journal. The Aboriginal Research Assistant directly communicated with talks and posters with mothers, health workers, council members and Aboriginal politicians.

Future Directions

A simple and quick method of gestational age estimation for Aboriginal infants has been designed and an evaluation using different observers should be completed this year.

This project has been funded by PHRDC and an NHMRC application for continued funding has been made to study the impact of the social environment on the long term consequences of IUGR and preterm infants and their possible relationships to adult disease. Children will be examined and measures of lung function, blood pressure, growth, nutrition, social factors and possible markers of chronic disease will be investigated.

TOXINOLOGY & TOXICOLOGY

Bush Medicines

In 1994, Dr Mark Myerscough commenced a Master of Medicine degree by research on the biological activity of some Tiwi medicinal plants. This study has been fully supported by the Tiwi people who have assisted in the selection and collection of plants, and the preparation of traditional remedies. In particular we would like to acknowledge the assistance of Tommy Daniels from Milikapiti; Anita Pangiramirri, Lydia Burak and Cornelia Tipuamantumirri from Pirlingimpi; and Ruth Kerinaia, Peggy Margaret Orsto, Judy Munkara and Antonia Kerinaia from Nguuu.

Twelve plants that are commonly used in the community, or considered particularly effective treatments, were selected for the study. Specimens of each plant were collected and passed on to the Northern Territory Conservation Commission for identification, and literature reviews were undertaken on the ethnomedical uses, pharmacological activity and chemical constituents of each species. Nine species and eleven extracts (three from different parts of the same species) were tested for antibacterial activity. Plants that are documented as being used for skin sores or scabies were also tested for activity against the scabies mite.

Five of seven extracts prepared by the Tiwi for use on skin sores and scabies had activity against *Staphylococcus aureus*, however only two had activity against *Streptococcus pyogenes*, the organism responsible for the majority of skin sores in Aboriginal communities. None of the plants had activity against scabies. This may be related to the recent introduction of the scabies mite to the Tiwi Islands; the first documented cases of scabies in the Northern Territory were during World War II, and some Tiwi believe that "Cyclone Tracy brought this illness". More concentrated extracts of the plants were prepared in the laboratory by boiling them in water. The activity of each of the Tiwi prepared extracts used for skin sores was confirmed with a series of dilutions of the concentrated extracts.

Of the three plants commonly used for respiratory complaints, just one had activity - and only against one organism. However, all of them had activity against some bacteria that commonly cause chest infections when tested with more concentrated laboratory preparations. The significance of these results is difficult to determine. One of the extracts has been separated into fractions by AMRAD and further testing will determine whether it will be worthwhile to attempt to identify its active constituent(s). Further assessment of the biological activity of these plants may also include antiviral testing and screening against a series of molecular targets routinely used by AMRAD as part of their natural products screening program.

Mark completed his study on Tiwi medicinal plants in mid-1997, reporting his results back to the Tiwi community via letters and a visit to the Health Board, Local Government and Land Councils. His thesis entitled "*The Biological Activity of some Tiwi Medicinal Plants*" recently passed examination.

This work was undertaken in collaboration with, and partially funded by, the AMRAD Corporation.

Snakebites

Since late 1989 we have been conducting a prospective study of snakebite in the top end. There have been 349 cases of suspected snakebite admitted to Royal Darwin Hospital included in the study. This is the largest prospective study of snakebite ever undertaken in Australia. The aim is to improve management of snakebite [21] and to better understand the envenoming processes for the important snakes in our region; the western brown snake, the mulga snake, the death adder and the taipan. Other lesser venomous snakes, such as the whip snakes, are also being studied. Altogether 95 cases of envenoming have been documented. The snakebite study is in collaboration with Professor David Warrell, Oxford University; Dr David Theakston, Liverpool School of Tropical Medicine; and Dr Julian White and Vaughan Williams at Adelaide Woman's and Children's Hospital. Paul Horner at Museums and Art Galleries of the Northern Territory, local snake expert Graeme Gow, NT Parks and Wildlife staff such as Dave Heard, RDH and Rural Services and Community Health Centre staff and GPs such as Dr Martin Muis



have been much appreciated sources of knowledge and help. Immunoassays for quantifying venom levels in blood have enabled studies on the efficacy of first aid and the response, measured by venom clearance, to various doses of antivenom. Because of the wide range of highly venomous Australasian elapids present in the Top End of the NT we have a unique opportunity to verify aspects of snakebite management which to date have been based on anecdotal experience. Preliminary results suggest current first aid methods are unfortunately usually ineffective, and required doses of antivenom are difficult to predict, and not always as suggested from anecdotal reports in the medical and lay literature.

Table 3. Summary of clinical features of bites from NT snakes

	Early Collapse	Local swelling	Tender regional lymph nodes	“Systemic signs”*	Myo-toxicity	Coagulo-pathy	Neuro-toxicity
Brown snake	++	+/-	+/-	+/-	-	++++	rare
Mulga snake	-	+++	+++	++	+++	+/-	rare
Death adder	-	++	++	+	-	-	++
Taipan	++	+	+	++	+	++	++
Whip snakes	-	++	+++	+/-	-	-	-

*Abdominal pain, nausea, vomiting, headache

This work is supported by the Wellcome Trust of Great Britain.

Jellyfish

In collaboration with Phil Alderslade at the Museums and Art Galleries of the Northern Territory; Dr Jackie Rifkin from Brisbane; Dr Peter Fenner and Dr John Williamson from the International Consortium on Jellyfish Stings; and Gabe Schraven from Gove Hospital Pathology, we have prospectively studied jellyfish stings in Top End coastal waters since 1989 [83, 151, 161]. Important findings to date include :

- Large numbers of potentially lethal box jellyfish (*Chiropsalmus sp.*) netted in a single location during some “safe” dry seasons (June - September).
- Significant stings occurring during “safe” dry seasons in Darwin.
- Confirmed stings from a new 4-tentacled box jellyfish (*Carybdeid* variety) yet to be named, but called the “Darwin Carybdeid”.
- Mild stings from *Chironex fleckeri* responding to therapy with ice.
- Cardiac abnormalities on ECG occurring with even some moderate stings from *C. fleckeri*.
- Vinegar being definitely superior to all other remedies tested to date, including several local “bush” medicines, for inhibiting discharge of nematocysts (stinging cells) of *C. fleckeri*. However several beverages common at beaches, such as Coca Cola and old wine, are of limited benefit.

Studies of clinical effects and treatment of snakebites and jellyfish stings continue.

Manganese and the Groote Eylandt study

From 1990 to 1997, Dr Tim Burt undertook his PhD thesis on the neurological disease known as the “Groote Eylandt Syndrome” and the health effects of manganese; manganese toxicity having previously been associated with neuropsychiatric and movement disorders overseas.

For some years certain family groups on Groote Eylandt and the Arnhem Land coast had been known to be affected by various neurological problems collectively termed the “Groote Eylandt Syndrome”. A number of funded studies had not resulted in a definitive answer to the cause of the problems, but some authorities claimed a relationship to the mining of manganese on the island to be important.

The loco-motor disorders had various presentations leading to difficulties in diagnosing whether the observed symptoms were different forms of the same condition or entirely separate entities. The main disorder usually presented in people aged in their mid-thirties with truncal ataxia and a heaviness or stiffness in the legs, progressing to nystagmus, weakness, decreased vibration sense and sometimes autonomic features. The sexes were equally affected with no definite occupational or other environmental association.

Our studies followed on from work done by Dr Charles Kilburn and showed significantly elevated blood manganese levels both on Groote Eylandt and in the East Arnhem region, however no difference was found between those with or without the neurological disease. Many of the other features present in the affected people, such as upper motor neurone signs, dorsal column signs, ophthalmoplegia and brainstem atrophy on central nervous system imaging, familial clustering and the lack of consistent occupational and environmental history also disputed manganese poisoning. In fact, we were unable to demonstrate any definite clinical significance of the elevated manganese levels, the cause of which is unknown - although environmental exposure seems most likely. Exclusion of significant abnormalities from the manganese exposure would require comprehensive and sophisticated studies.

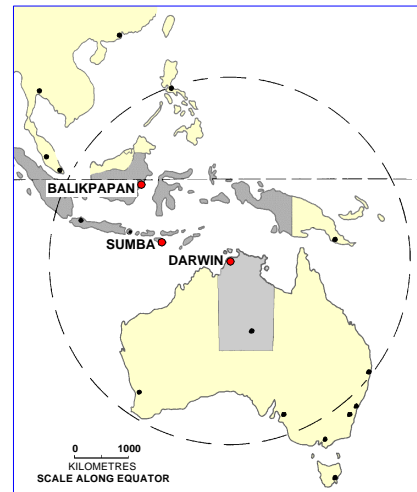
Clinical and pathological features and an autosomal dominant inheritance suggested the illness to be Machado-Joseph Disease [12], a degenerative condition of Portuguese origin. From 1992- with community and individual consent, studies on the genetic basis and clinical nature of Machado-Joseph Disease were undertaken in collaboration with Prof Garth Nicholson from Sydney, Drs Jon Currie and Paul Maruff from the Victorian Mental Health Research Institute, and Prof Peter Blumbergs from the IMVS in Adelaide [246]. These studies confirmed that “Groote Eylandt Syndrome” was Machado-Joseph Disease [221]. More recently the abnormal gene for MJD was identified overseas to be on the short arm of chromosome 14, and the specific abnormality was also confirmed for the NT cases.

Tim’s study of the “Groote Eylandt Syndrome”, together with his studies of the health impact of high blood levels of manganese found in the Arnhem Land region were documented in his thesis, entitled “*Health Effects of Manganese Exposure in East Arnhem Land*” which was successfully completed in 1997. Resources should now be directed towards assisting and providing genetic counselling for the affected families and support for those with progressive disabilities and their families

This work was supported by The Groote Eylandt Community Trust, the Groote Eylandt Mining Company (GEMCO), and Territory Health Services.

INTERNATIONAL HEALTH

In 1996, to mark the 50th anniversary of Indonesian Independence, and with the support of the Indonesian Ministry of Health, the Northern Territory Government provided funding for two Fellowships, for research in cooperation with Indonesian health authorities towards the better understanding, prevention and treatment of malaria and tuberculosis in the Eastern Provinces of Indonesia. The initiative also sought to enhance malaria and tuberculosis research capabilities in Eastern Indonesia.



Much early work in 1996-97 involved extensive consultations with multiple sections of the Indonesian Ministry of Health at a national, provincial and district level, to identify the Eastern Province-based research fellow and to establish the process, structure, agenda and priorities for the research collaboration. This process is continuing.

In July 1997, the Darwin-based Research Fellow, Nick Anstey was joined by the Eastern Province-based Research Fellow, Emiliana Tjitra, who was seconded from the National Institute for Health Research and Development in Jakarta. After working in Nusa Tenggara Timur Province for several years in the 1980's Emiliana has continued to be involved in multiple malaria field studies in Eastern Indonesia. She is working in collaboration with Nick Anstey and Bart Currie towards a PhD. A number of studies are now underway:

Studies of Clinical Epidemiology of Malaria and New Methods of Diagnosis

Emiliana Tjitra, has recently completed the first of her malaria field studies in West Sumba in Nusa Tenggara Timur (NTT) Province (September 1997-May 1998). These studies are examining how clinical manifestations and predictors of malaria and their immunological correlates vary among areas with different malaria transmission intensity, with different levels of immunity and in different age groups. These studies will evaluate the utility of current Ministry of Health case definitions for clinical malaria for individual case diagnosis/management and for disease surveillance in regions with different malaria epidemiology. This is important in a country like Indonesia, with malaria transmission ranging from zero through to hyperendemicity.

One of the aims of these studies is to improve the accuracy of malaria diagnosis. In collaboration with the Indonesian Ministry of Health, she has coordinated refresher and retraining sessions for local health centre, hospital and district microscopists. Problems with access to prompt and reliable microscopy have limited the usefulness of microscopy in malaria-endemic countries. Previous studies in Indonesia and elsewhere have shown the utility of rapid antigen detection methods for diagnosis of falciparum malaria, but these have been limited by the inability to also diagnose vivax malaria. In parallel with the above studies she has also been evaluating the diagnostic usefulness in the field of

new prototype rapid combined *P. falciparum* / *P. vivax* immunochromatographic antigen detection tests. Preliminary results show sensitivity for both species of malaria.

Dr Tjitra is also using the new 1996 WHO protocol to evaluate in vivo drug resistance patterns for both major species of malaria in the study areas. These have confirmed widespread chloroquine resistance in West Sumba as in other areas of eastern Indonesia. It is hoped that 1998-99 studies at the second field site with more intense malaria transmission intensity will also include open safety and efficacy evaluations of new WHO combination drug regimens for uncomplicated clinical malaria, that are undergoing multicentre evaluation of their ability to slow progression of drug resistance.

Funding for this work is provided by the Northern Territory Government Malaria-Tuberculosis Research Fellowships; ICT Diagnostics; Mark Nicholson and Alice Hill.

Nitric Oxide (NO) in Severe and Uncomplicated Adult Malaria

This study in Balikpapan, East Kalimantan Province is extending previous work into the role of nitric oxide (NO) in the immune response to *Plasmodium* infection and in the pathophysiology of severe malaria [274, 330, 331, 332]. In Tanzanian children we have previously shown that NO production/leucocyte inducible nitric oxide synthase (NOS2) expression is inversely associated with disease severity; with levels being highest in healthy malaria-exposed children with asymptomatic parasitaemia and lowest in those with fatal cerebral malaria [*J Exp Med*, 1996; 184: 557-567]. While NO production is associated with protective rather than pathological host responses in semi-immune East African children, it is important to know whether this association is also evident in non-immune adults from a region such as East Kalimantan with different malaria epidemiology. Nick Anstey and Emiliana Tjitra are collaborating with Dr Sumarjati (Ministry of Health) and local researchers supported by the study (Dr Oey Tjeng Sien and Dr Ating Solihin) at Balikpapan General Hospital and Indonesian Timber Corporation Hospital. We are recruiting patients with severe and cerebral malaria, uncomplicated malaria, asymptomatic parasitaemia and healthy controls. Recruitment commenced in June 1998. We will be measuring nitric oxide metabolites, mononuclear cell NOS2 expression and activity, and other measures of NO production [274, 351] in each study group, correlating these measurements with production/expression of selected T1 and T2 cytokines. This research may have important therapeutic implications for management and prevention of severe malaria in the future. Dr Jocelyn Saunders has recently joined Menzies from the US and is leading the laboratory studies for this project. Estelle Gray is providing technical assistance. A Ministry of Health laboratory technologist will be trained in these techniques as they are performed at MSHR

Funding for this work is provided by a National Institutes of Health (USA) grant (1997-2002).

S-Nitrosothiols and Malaria : Potential Disease-Modifying Effects

In complementary laboratory studies, Nick Anstey, Jocelyn Saunders and Estelle Gray are collaborating with Katharine Trenholme in the Molecular Parasitology Unit to examine whether the nitric oxide donors S-nitrosothiols (RSNOs) prevent processes linked to the pathogenesis of severe malaria. We are determining whether nitric oxide inhibits/prevents cytoadherence of parasitised red cells (PRBC) to endothelial cells, melanoma cells and non-infected red cells, and whether nitric oxide can prevent or inhibit malaria parasites from stimulating production of disease-causing cytokines, such as TNF. Our preliminary studies show that RSNOs inhibit parasite invasion and growth within

red cells. While treated melanoma cells still bind to PRBC, RSNO treatment of PRBC inhibits cytoadherence to melanoma cells at least at supraphysiological concentrations. These studies are important in understanding the potential role of NO-related molecules in protection from disease, and may have therapeutic implications.

Funding for this work has been secured by a grant from the Australian NHMRC (1998-2000).

Tuberculosis Drug Resistance in Timor

Following extensive discussions with national and provincial staff from the Indonesian Ministry of Health Sub-directorate of Tuberculosis Control, WHO TB representatives in Jakarta and Provincial Disease Control/ Reference Laboratory in Kupang, and in collaboration with Dr Vicki Krause, Disease Control, Territory Health Services, we submitted in 1997 a collaborative tuberculosis project proposal to AusAID that included both operational research and programmatic components. Following review by AusAID and WHO's Global Tuberculosis Programme this proposal has now been incorporated into an AusAID-funded WHO project to improve implementation of WHO's DOTS strategy and operational research in West and East Timor (proposal on file at MSHR). Following recent approval by the Indonesian planning Ministry BAPPENAS, it is anticipated that this project will start later in 1998. MSHR is listed as the Institution coordinating and performing the studies of TB-drug resistance, which will also involve training of Timorese in the skills required for the laboratory and programmatic aspects of the project in both Kupang and Darwin.

Other Work

We will be collaborating with the Molecular Parasitology Unit (see MPU report) to link their recent CLAG findings to the field. The Molecular Parasitology Unit will soon be examining sera from Tanzanian adults to determine if antibodies to CLAG are present in malaria endemic areas, and will also determine if there are serological differences in CLAG recognition among children with and without cerebral malaria. Retrospective serological analysis in our previously-described Tanzanian study group will be complemented by prospective studies in Indonesia from areas with different malaria epidemiology and parasite genetics.

Significant Collaborations

Nitric oxide and malaria

We are collaborating with Professor J Brice Weinberg (Duke University Medical Center, Durham, NC, USA) who is undertaking further studies in our group of Tanzanian children with and without cerebral malaria to explore potential mechanisms for the suppression of NO production/ mononuclear cell NOS2 expression in cerebral malaria and increased production in subclinical malaria. Professor Donald Granger and Dr Maurine Hobbs (University of Utah Medical Center, Salt Lake City, Utah, USA) are studying genetic polymorphisms in the Tanzanian study group that may explain these differences in NO production. These studies have implications for prospective studies in Indonesia.

Nitric oxide and gut permeability in paediatric gastroenteritis/malnutrition

Systemic NO production has previously been shown to be markedly elevated in adult gastroenteritis, and NO has been implicated in animal studies as a mediator of altered gut permeability during inflammation. We are collaborating with Professor David

Brewster and Dr Renata Kukoruzovic (Flinders Clinical School and Dept Paediatrics, Royal Darwin Hospital) to correlate systemic NO production and mononuclear cell NOS2 expression with severity of paediatric gastroenteritis as measured clinically and by dual sugar permeability studies. This will allow us to longitudinally correlate gut function and structural integrity with gut inflammation. Our preliminary studies show similar marked elevation of NO production in paediatric gastroenteritis. Apparently healthy children living in malaria-endemic tropical environments have chronically elevated NO production/NOS2 expression that is associated with anaemia [330]. We are examining whether similar results are found in Top End children currently being recruited as control children for this study who are exposed to a non-malarious tropical environment. NO production as a measure of inflammation will be used as one of the outcomes in randomised controlled intervention studies to assess the effects of various interventions on gut inflammation and clinical outcome.

These NO studies are supported by the NHMRC Centre for Clinical Excellence, which includes Bart Currie and Nick Anstey as Investigators.



Ear Health and Education Unit

Al Yonovitz

Otitis media (middle ear disease) and associated conductive hearing loss affect most Aboriginal children and adults during their life. The educational, social, and economic impact of this disease has implications for the advancement of Aboriginal Australians living in rural and remote communities in the Northern Territory. The aim of the Unit is to apply multidisciplinary research to address the natural history, prevention, treatment and habilitation of ear disease and its sequelae. We support collaborating Aboriginal communities in identifying desirable outcomes for health care and long-term social benefits, and also work closely with Territory Health Services, the Aboriginal Hearing Program and the Australian Hearing Services. Results from our research contribute to improved health education and skill development for Aboriginal and non-Aboriginal health staff working within the Northern Territory.

*Our efforts over the past five years have been guided by the findings of our important 1993 study that demonstrated the very early onset of otitis media in Aboriginal children. Within 30 days of birth 60% of infants have otitis media, and by 60 days, 90% are affected. The concurrent microbiological studies of the nasopharynx found that the colonisation rate was 46% for *Moraxella catarrhalis* and 24% for each of *Streptococcus pneumoniae* and *Haemophilus influenzae* by 30 days of age. Associated hearing loss from this very young age places infants and children at very high risk for auditory, language and educational disability that may persist throughout their lives.*

The Unit's program of research reflects a comprehensive approach to ear health. Important new themes include the relationship between early onset and persistent ear disease to chronic respiratory disease, the epidemiology of antibiotic resistance, and the role of personal and community development in the translation of research findings into improved health services.

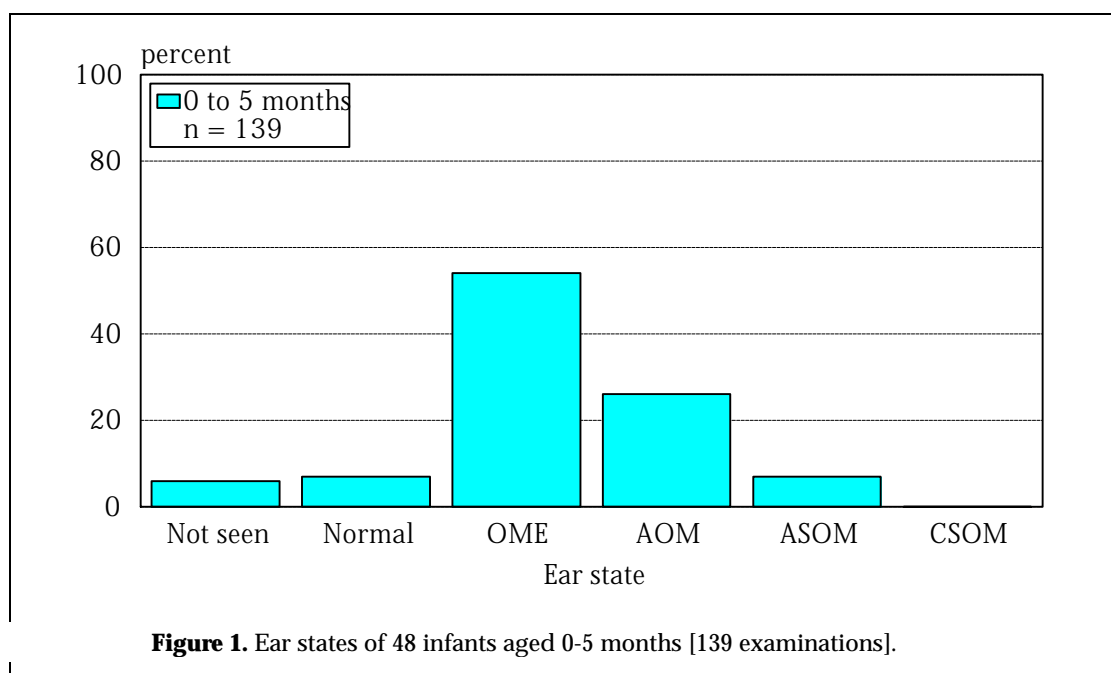
MEDICAL ASPECTS OF DISEASE

Otitis media (OM) is frequently a chronic bacterial disease in high risk populations and is associated with high rates of other bacterial respiratory infections. Medical interventions have much to offer.

Antibiotic vs Placebo for Prevention of Chronic Otitis Media

Our first randomised, placebo-controlled, trial (RCT) to be undertaken with remote area Aboriginal children was initiated in 1996. The study is triple-blinded and will provide the highest quality evidence regarding early intervention with antibiotics. The rationale for this study was developed from earlier work describing the natural history of otitis media and pilot trials of recommended antibiotic regimens [102]. Published meta-analyses had indicated that high risk populations were most likely to benefit from antibiotic use. However, increasing concern regarding antibiotic resistance demands evaluation of the benefits vs costs of such therapy. In the first year of the RCT 317 ear examinations occurred in 48 infants. Middle ear disease was detected in over 90 percent of examinations, and rates of acute infection and perforations were high (see **Figure 1** below). This occurred despite the frequent use of antibiotics.

This study has formed the core of our recent research and inspired many of the technical and scientific advances being adopted by additional research projects and proposals. Amanda Leach is the Chief Investigator and, together with Tania Shelby-James and Grace Perez, is responsible for microbiological work. Peter Morris is the medical officer responsible for diagnosis and medical management. Al Yonovitz provides the audiological expertise. Harold Koops, Angela Melder, and Leslie Yonovitz support the Tiwi “dosing team” and share important information with families to ensure that they have a good understanding of the study. Harold Koops is also responsible for introducing the study to other communities. Patrick Scott and Aaron Leach provide data management, computer programming and video editing skills. This research is supported by the NHMRC.



Chronic Suppurative Otitis Media (CSOM) - Can Compliance be Improved?

CSOM is the most important cause of childhood hearing impairment in developing countries and NT Aboriginal communities. The disorder is associated with low socioeconomic conditions and usually follows inadequately treated or untreated acute otitis media (AOM). The disease can persist for months or years with increasing hearing

impairment and other infective complications. Chronicity may be related to low rates of compliance with medical therapy.

Children, aged 3-16 with middle ear disorder, were identified through screening (tympanometry, otoscopy and audiologic testing) at the two Bathurst Island schools (Murrupurtiyanuwu Primary School and the Xavior Catholic School). Methods for diagnosis included case history, pneumatic video otoscopy and acoustic impedance (tympanograms) measures. The 50 children with CSOM were randomised into the following 4 groups in a double blind, placebo controlled randomised clinical trial using a factorial design:

- Group 1: Compliance/Adherence education and electronic/computer devices
Topical antibiotic plus oral antibiotic (amoxycillin)
- Group 2: Compliance/Adherence education and electronic/computer devices
Topical antibiotic plus oral placebo
- Group 3: Standard clinical instructions
Topical antibiotic plus oral antibiotic (amoxycillin)
- Group 4: Standard clinical instructions
Topical antibiotic plus oral placebo

Half of the participants (parents or caregivers) were given instructions for providing the oral (amoxil or placebo) plus topical antibiotics (gramicidin-framycetin-dexamethasone) consistent with standard practise in the health clinic. This included a discussion of the diagnosis, recommended treatment, and the need for a follow-up appointments. The remaining half of the subjects (parents or caregivers) were also shown a video tape, encouraged to ask questions, and given computer/electronic devices to aid in compliance and monitoring. In addition to the otologic measures nasopharyngeal and ear discharge swabs were obtained for microbiological analysis. The period of treatment was 6 weeks with an evaluation similar to the pre-antibiotic regimen occurring every 2 weeks and included a 12 week follow-up. The results of this important study should help improve CSOM treatment and have implications for school based programs. The analysis of the data is continuing. The research was supported by Merck, Sharpe and Dohme.

Investigation of Otitis Media and Pneumococcal Carriage in Child Care Centres

Sue Skull, Centre for Disease Control and MAE scholar with NCEPH, in collaboration with other staff from Territory Health Services (THS) and the Ear Health and Education Unit conducted a longitudinal study examining the incidence of otitis media and levels of *Streptococcus pneumoniae* (*Spn*) carriage and antibiotic resistance in Darwin child care centres. Prior to this study, it was thought that Australia had relatively low rates of pneumococcal penicillin resistance. It is now clear that the rapid rise in pneumococcal resistance seen elsewhere has begun.

The prospective cohort study of 251 children under 4 years of age in 9 Darwin child care centres was conducted between 10 March 1997 and 15 September 1997. Each fortnight, nasopharyngeal swabs, video-otoscopic images and tympanograms were collected from children and parents interviewed about medications administered. Based upon the number of Type B tympanograms, effusion was detected in 37% of all examinations conducted. Risk factors associated with middle ear effusion (MEE) were previous grommets, ethnicity, younger age, the child care centre attended and a family history of ear infection. This is clinically important, since MEE and associated hearing loss during early childhood may affect learning and speech development. Overall, 52% (1026/1977) of nasal swabs were positive for *Streptococcus pneumoniae*. Average carriage rate varied

between centres (41% to 71%) and between fortnights (45% to 67%). Resistance to penicillin or oxacillin was found in 31% of swabs, to tetracycline in 17%, to erythromycin in 17%, to cotrimoxazole in 45% and to chloramphenicol in 12%; 18% of isolates were multiresistant, 25% had intermediate resistance and 2.6% had high level resistance to penicillin. A minimum of 13% of isolates had intermediate ceftriaxone resistance and 0.3% had high level resistance. The proportion of pneumococcal carriers with penicillin resistant strains showed a remarkable variation of between 0% and 63% and multidrug-resistant strain carriage varied from 0% for one centre to 50% for another. Preliminary results from serotyping 305 isolates indicate that multidrug-resistance was primarily associated with serotype 6B however some strains belonging to serotypes 6A, 23F, 19F and 19A were also multidrug resistant. Nineteen serotypes (13 groups) were found, 78% of isolates belonged to serotypes 6A, 6B, 19F, 19A, 14 and 23F. Vaccine strains accounted for only 50.5% of isolates although a further 34.7% were either 6A or 19A which are closely related to vaccine strains 6B and 19F although recent evidence fails to demonstrate cross protection. The average fortnightly proportion of children given antibiotics was 16.4%. Perhaps paradoxically, the centre with no resistant strains identified to date was the centre with the highest recorded levels of antibiotic use. Further laboratory and statistical analyses are required before conclusions can be drawn from this data. Nonetheless, levels of intermediate and high level penicillin resistance in this NT population are greater than any previously published in Australia (7.6% of non-invasive isolates) and may herald the onset of a national rise in pneumococcal resistance similar to that seen in other countries. We must continue to promote the judicious use of antibiotics and to pursue conjugate pneumococcal vaccine as an avenue for managing pneumococcal infections and middle ear disease [386B].

MICROBIOLOGICAL ASPECTS OF DISEASE : “EARLY, MULTIPLE, DENSE & RESISTANT”

A better understanding of the biology of disease helps to explain the potential benefit and limitations of medical interventions. The particular features of respiratory bacterial pathogen carriage in this population, which we suggest helps to explain the chronicity of infection, have been :

- 1. the very early age of acquisition [102];*
- 2. the multiplicity of strains that may be carried concurrently; and*
- 3. the colonisation density.*

Neonatal Acquisition of Respiratory Bacterial Pathogens and Onset of Persistent Otitis Media

We have reported the findings of a longitudinal study of otitis media and nasopharyngeal respiratory microbiology from birth; nasopharyngeal colonisation with bacterial respiratory pathogens *Moraxella (Branhamella) catarrhalis*, *Streptococcus pneumoniae* and non-capsular *Haemophilus influenzae* (NCHi) was predictive of early onset otitis media in Aboriginal infants. Multivariate analysis showed that while both onset of OM and acquisition of bacterial pathogens in the nasopharynx were age related, onset of OM was better explained by bacterial colonisation than by age. Further support for a bacterial aetiology of OM came from results of ear discharge culture; 30% of infants experienced perforation(s) during the first six months of life [216] and 67% of these yielded *S. pneumoniae* and/or *H. influenzae* (more rarely *M. catarrhalis*).

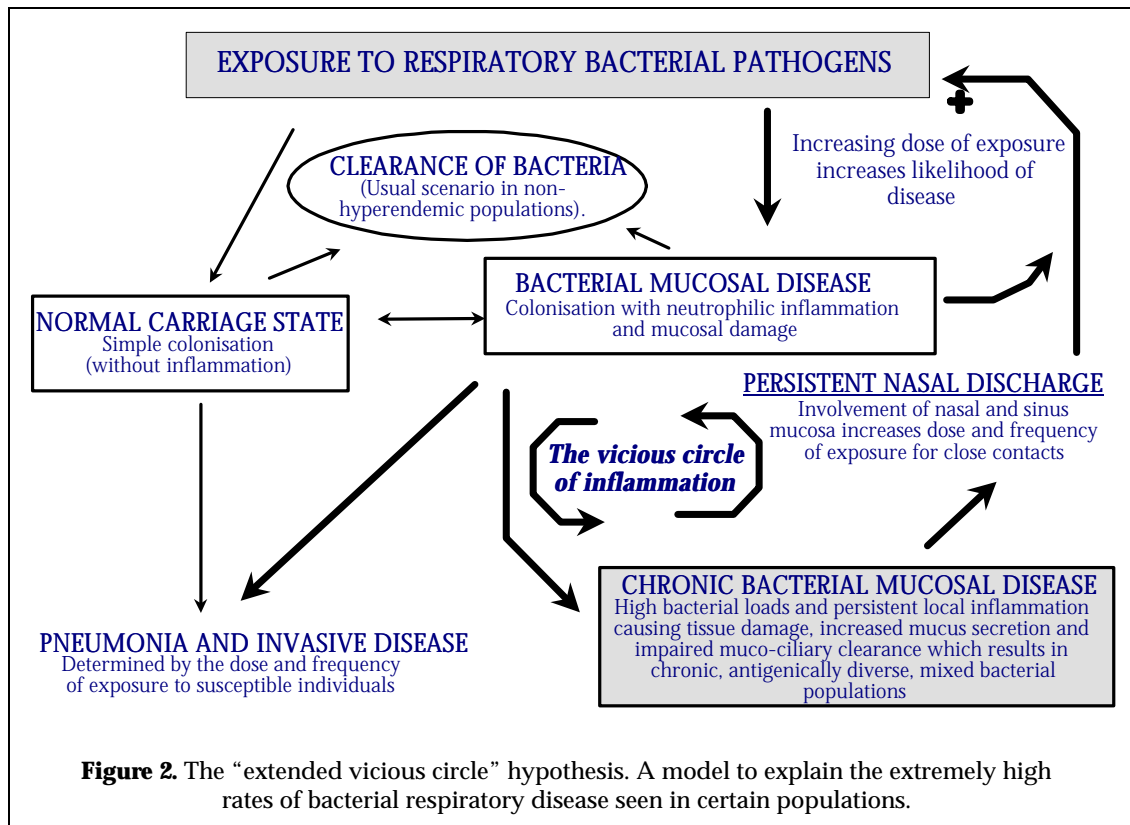
Treatment of Otitis Media

In pilot randomised trials we found that short courses of antibiotics were ineffective in curing otitis media (AOM, OME or CSOM) or in eradicating respiratory bacterial pathogen carriage, however infants receiving up to 28 days amoxicillin experienced significantly later age of first tympanic membrane perforation than historical controls not receiving antibiotics. These findings emphasise the need for well designed clinical trials to confirm the potential role of antibiotics in the management of otitis media in Aboriginal children.

Understanding the Endemicity of Respiratory Bacterial Infection

The multiplicity of bacterial species carried in the nasopharynx was a significant differentiating characteristic between Aboriginal and non-Aboriginal infants. Non-Aboriginal infants were colonised by single species (*M. catarrhalis*) and experienced transient episodes of OM compared to Aboriginal infants where infection with two or three species was established early in life and persisted. The diversity of strains and types within each species in this population contributed to the maintenance of high carriage rates of each species, possibly supported by some degree of antigenic tolerance following presentation in infancy. At least 30 different pneumococcal serotypes and 50 different strains of NCHi [259] were found in the infants living in the community studied. With up to four colonies of each species per swab selected for typing, concurrent carriage of multiple types was also detected. The presence of different serotypes in swabs collected monthly, or more frequently, suggests that strains may be accumulating since the immune responses required for rapid clearance are unlikely to be developed in the very young infant. Important evidence that strains co-colonise at ratios of several hundred to one was documented through the use of selective media (see below). We suggest that concurrent carriage of dominant and "hidden" strains is a mechanism that ensures that each strain is maintained in an individual for long enough to be transmitted to susceptible newborns, thus sustaining endemicity. Mathematical models are consistent with multiple endemic strains being maintained in small populations through concurrent carriage of cooperating strains in individuals, but suggest that partial competitive exclusion of other strains by the strains already carried also occurs.

Rates of invasive pneumococcal disease in under 2 year olds are 12 to 80 times higher in Aboriginal children than in developed countries. Persistent nasal discharge, however, peaks at a later age. It may be that the greatest risk factor for invasive disease in under 2 year olds is exposure to persistent nasal discharge (dense carriage of multiple bacterial respiratory pathogens) in older children. This hypothesis has important implications for the management and prevention of invasive disease in infants, and well designed intervention studies are needed to it.



Antibiotic Resistance

The role of antibiotics in Aboriginal communities with high rates of bacterial infection, including persistent asymptomatic otitis media (AOM), needs urgent evaluation. We are currently conducting a blinded randomised placebo-controlled trial of amoxicillin for the treatment of OME and prevention of CSOM. In pilot studies of otitis media therapy the impact of antibiotics on the dominance and transmission of a pre-existing multidrug resistant (MR*Spn*) serotype 6B clone was studied. A selective medium was used which allowed detection and (semi) quantitation of both resistant and sensitive strains in single specimens [179]. This confirmed that multiple types of pneumococci co-colonise the nasopharynx and that a clone (in this case MR*Spn*) may be present in the nasopharynx in low numbers, "hidden" by a greater density of (dominant) pneumococcal clones. This theory was further developed in a carriage study conducted in conjunction with a community-based trachoma intervention program where a single dose of azithromycin was given to all children with trachoma and their childhood contacts [298]. The pneumococcal carriage rate was reduced from 68% to 29%. However the proportion of pneumococci with azithromycin-resistance increased from 1.9% to 54.5%. We noted that the children in whom resistant strains were first detected had been colonised by non-resistant strains at the time of treatment whereas children not colonised by pneumococci at the time of treatment acquired resistant strains at a slower rate. It was therefore postulated that resistant strains, already present in colonised children but "hidden" by dominant strain(s), gained a selective advantage following eradication of the dominant azithromycin-sensitive type(s).

This study was also important in demonstrating that high rates of resistant strain carriage could not be maintained following cessation of antibiotic use, presumably due to overgrowth by sensitive strains. The "disappearance" of resistant strains in the absence of azithromycin was rapid in this population. In populations with fewer exposures,

(lower pneumococcal carriage rates and improved living conditions), this overgrowth may not be as rapid and resistant strains may persist due to the reduced competition from sensitive strains.

Models for Endemic Carriage of Multiple Strain Organisms

Mathematical modelling is an exciting new discipline in public health and will be used increasingly in the future. Global strategies for the control of pneumococcal infection must be firmly based on a quantitative understanding of the biology and epidemiology of pneumococci. Simple mathematical models have been developed to explain carriage, transmission and the apparent stability of endemic carriage of large numbers of strains, even in small populations. John Mathews, Amanda Leach, Paulette Lieby, and James McBroom will continue to refine their models as more data become available.

Haemophilus influenzae

Non-encapsulated *Haemophilus influenzae* (NCHi) is also a major agent in the aetiology of otitis media. Heidi Smith-Vaughan and Louise Martin have been studying the carriage dynamics and genetic diversity of NCHi colonising the infants in the study. This work is described in the Molecular Parasitology Unit report.

Hib Carriage Increase

We reported a cumulative Hib carriage rate for the pre-conjugate vaccine era (1972-mid 1993) of approximately 42% in the first six months of life [387]. At this time (6 months prior to vaccine introduction) 15 cases of invasive Hib disease had been reported for the Northern Territory. Six months following commencement of infant Hib conjugate vaccine program for older infants and children, Hib carriage fell to almost zero and in 1994 no case of invasive Hib disease was reported. In 1996 cumulative Hib carriage was 30%. This observation remains unexplained; vaccine coverage has been high and cases of invasive disease rare (two cases in the Northern Territory during 1996). The possibility that the vaccine has provided a shorter duration of protection than predicted must be considered.

AUDIOLOGICAL ASPECTS OF DISEASE

While the most effective immediate interventions will be medical, the most important consequences of disease are related to the degree of hearing loss. For many Aboriginal Australians, the effects of ear disease persist throughout their life.

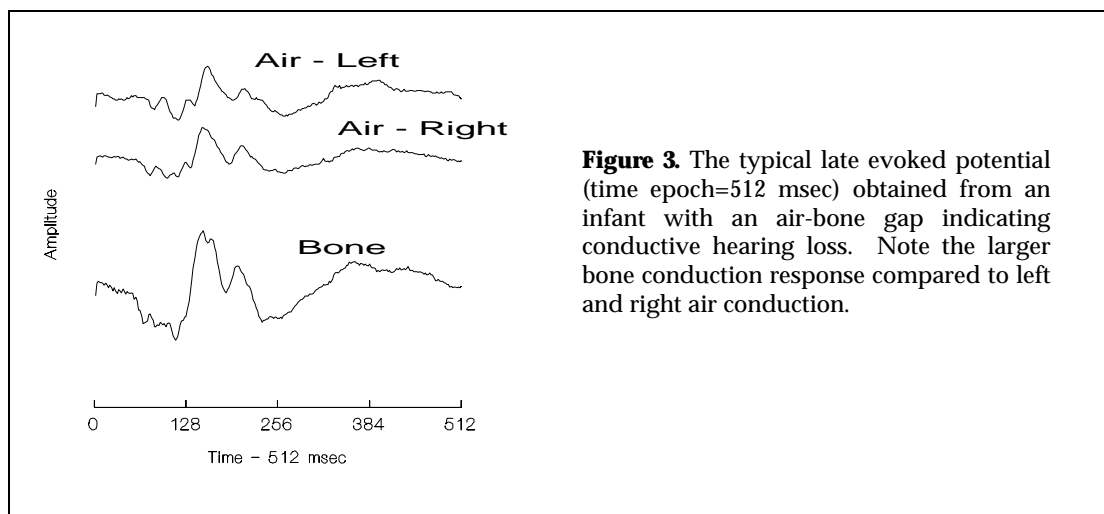
Masking Level Differences : Normative Values

The masking level difference (MLD) is a psychoacoustic measure of binaural interaction and central auditory processing related to extracting signals from noise backgrounds. The MLD is a more efficient and less culturally biased predictive measure in the assessment of auditory processing disorders. The MLD was investigated in normal hearing children who had no history of ear disease, aged 7 to 13 years. In the first MLD test, the masking noise was an interaurally in phase (No), 300 Hz noise band centred on 500 Hz. The 500 Hz pure tone signal was generated digitally and presented either interaurally in-phase (So) or 180° out of phase (S π). In the second MLD test, a 500 Hz pure tone signal was interaurally in phase (So) and the noise was either interaurally in phase (No) or 180° out of phase (N π). The data were collected using a simple up-down adaptive procedure. The

mean MLD was 11.0 dB (SD: 1.67) when the signal phase was changed, and it was 7.8 dB (SD: 1.75) when noise phase was changed. These data will provide normative values which will be used in audiological clinics throughout Australia. This research was supported by the Channel 7 Children's Research Fund.

The use of Late Evoked Potentials to Determine Conductive Hearing Loss

In our work on otitis media with effusion (OME) with Aboriginal infants and children we needed an objective method that would estimate the air-bone gap. The click stimuli associated with brainstem evoked potentials would not be sensitive to low frequency hearing deficits often associated with OME. Also, the low amplitude signals from brainstem evoked potentials might require a high number of trials and consequently lengthy sessions with infants. Late evoked potentials were utilised in a paradigm that minimises the deleterious effects of adaptation allowing a valid comparison between stimulus conditions that are continually changing in a random manner. The comparison of air conduction with bone conduction for each ear defines the air-bone gap which indicates the degree of conductive hearing loss (**Figure 3**). Preliminary data shows an excellent agreement with tympanometry and behavioural audiometry. The technique of concurrently averaging a number of conditions using computer technology is an innovative way of using late evoked potentials for the direct comparison of stimulus conditions. This research was supported by the NHMRC.



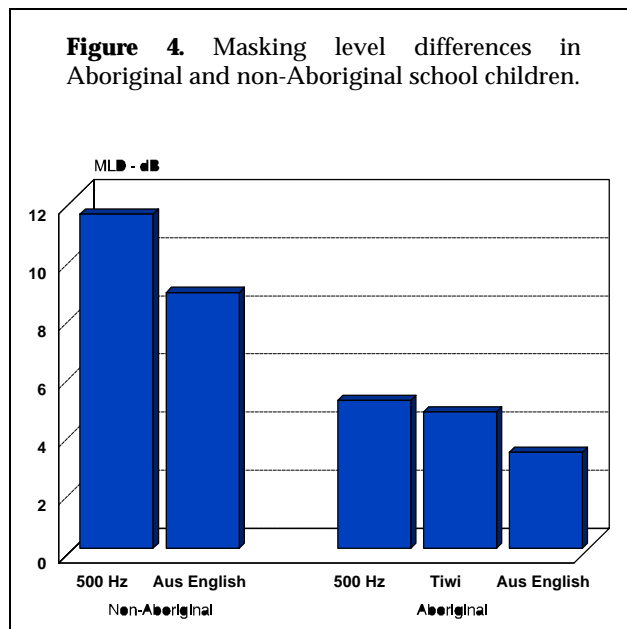
AB Word Lists : Normative Values

The AB words are widely used in audiological practice to determine word intelligibility. This is important in diagnosis and hearing aid fitting. Although the Performance-Intensity function for AB words has been determined, speech discrimination at various signal to noise ratios using these words has not been reported with the recent revisions to these lists. The revised National Acoustic Laboratory (NAL) AB words have been recorded on a CD and equalised using an A weighted Leq procedure, resulting in individual words having different peak values. Additionally, word order has been rearranged and low familiarity words have been replaced. This research determined in a sample (N=120) of children aged 6-13, speech discrimination performance using a white noise and speech spectrum maskers. Four signal to noise ratios (-10, -5, 0 and +5dB) were digitally mixed using the 15 AB word lists resulting in 120 lists. The study was initiated by Venkatesh Aithal and these results provide the first Australian norms for AB words in

noise. These norms will be incorporated in the general practice of Audiology throughout Australia.

Early-Onset Auditory Deprivation and Central Processing Disorders in Aboriginal Children

Deficits in auditory processing derive from the early-onset auditory deprivation related to a history of conductive hearing loss caused by otitis media with effusion (OME). The masking level difference (MLD) is a psychoacoustic measure of binaural interaction and central auditory processing related to extracting signals from noise backgrounds. The MLD was measured in two groups of children using speech and tonal stimuli. One group of children was Aboriginal, having a history of OME and speaking Tiwi as their first language and English as a school language. The comparison group of children with no history of OME was English-speaking non-Aboriginal. All were tested to obtain their MLD's to tonal and English stimuli. Aboriginal children were also presented with speech stimuli in Tiwi. The results indicated highly significant differences in the MLD between

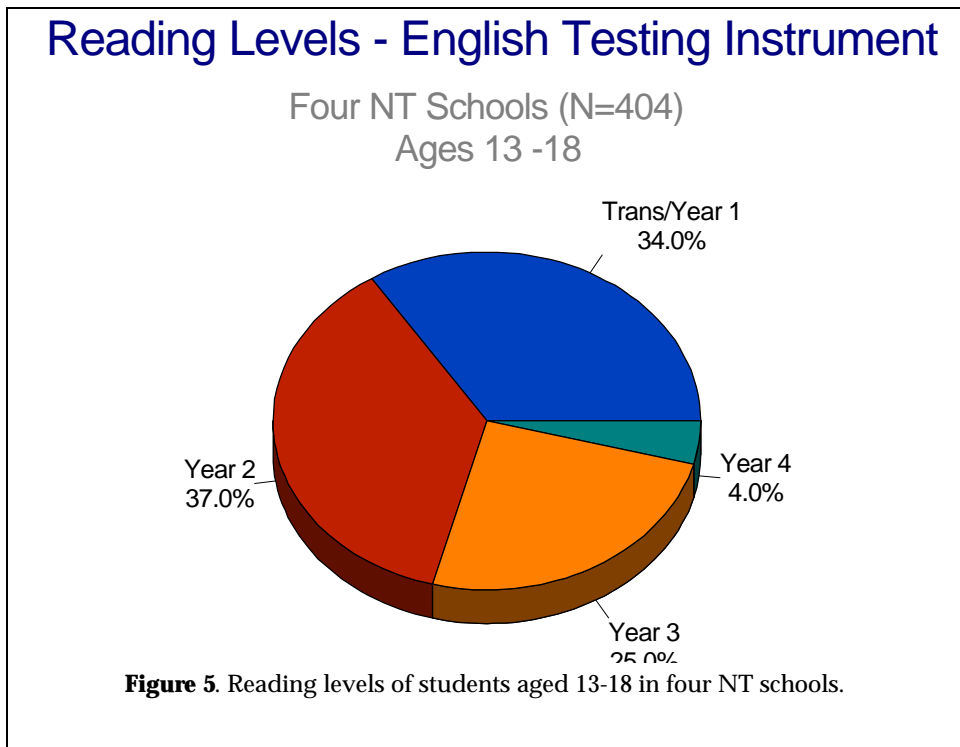


children with and without a history of OME, yet there was no significant difference between the Aboriginal children's MLD's for tonal and Tiwi stimuli (**Figure 4**). These findings indicate that Aboriginal children are at a disadvantage for listening to speech, particularly English, in noisy settings. This research was supported by the Channel 7 Children's Research Fund [271].

Advancing Indigenous Literacy through Support for Hearing Disabilities

This is a DEETYA funded strategic initiative which acknowledges that auditory processing deficits in addition to peripheral hearing loss are long-term

consequences of recurring otitis media during early childhood which is the critical period for language development. While Aboriginal children typically gain competence with basic interpersonal communication skills, they are at a distinct disadvantage for gaining English language literacy. The basis of the problem involves discrimination of English speech sounds and sound combinations that are not represented in Aboriginal languages. Indigenous students have also been found to be disadvantaged in extracting the speech signal from a noise background, making it difficult for them to understand their teachers in classroom settings. Aboriginal students in six independent schools are the focus of this strategic initiative to advance literacy through hearing support services. Leslie Yonovitz and Al Yonovitz are coordinating the project. Rebecca McCulloch is the project Educational Audiologist and Sharon Wynders is providing literacy support services to teachers at the Alice Spring and Ayers Rock School. Program evaluation data will be obtained from over 700 students in 39 classrooms. A majority of the students have already been given inventories to assess literacy (pre-measures) using an English language based test. See **Figure 5**.



Project components

- **Hearing support services** - audiometric testing, medical evaluation and coordination of treatment, sound field amplification systems in all classrooms, consultation regarding use of individual FM classroom hearing aides, school staff inservice and consultation.
- **Phonological awareness auditory training** - attention to speech sounds that are difficult to hear, different in English and Aboriginal languages, and in contexts that are particularly challenging for students learning English as a foreign language.
- **Health education** - the relationships between nutrition, cross-infection and hygiene, and hearing health and social disadvantage.
- **Community involvement in support of Indigenous literacy.**

The research is supported by DEETYA.

CROSS CULTURAL HEALTH CARE CHALLENGES

Health care interventions are likely to be most effective when they are evidence-based and when they meet the perceived needs of the individuals and communities at risk.

Health Communication

This is a discourse genre analysed in terms of communication roles people assume in conversations about health and health care. Systematic discourse analysis helps identify cultural influences that explain otherwise puzzling behaviour, such as non-compliance with medication, absconding from hospital, and refusal of treatment for mental illness or

substance abuse. Leslie Yonovitz has been conducting observations of health communication while living in an Aboriginal community and participating in Ear Unit research.

Compliance/Adherence Issues

Angela Melder is studying the health beliefs of Tiwi Aboriginal people as part of her MPH treatise being supervised by Dr Peter d'Abbs. Angela is using qualitative research methods to describe the way that attitudes and beliefs of participants and researchers could affect the implementation and the outcomes of a medical research study. She is examining the social context of our current clinical trial and helping to determine how efficacy studies in rural Aboriginal communities should be interpreted and, hopefully, improved.

Informed Consent

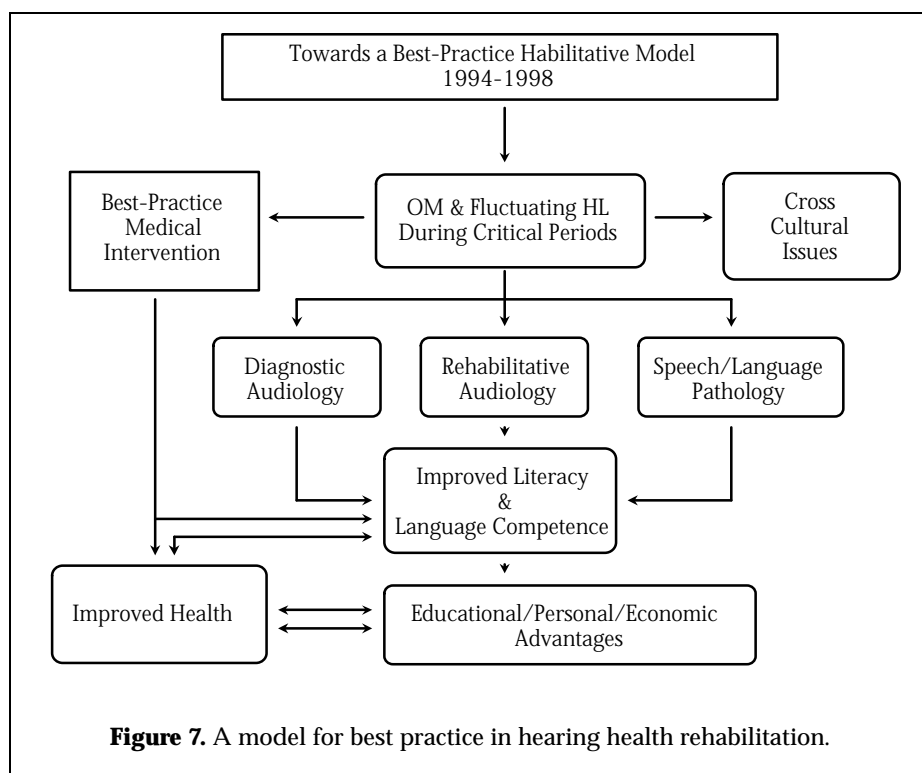
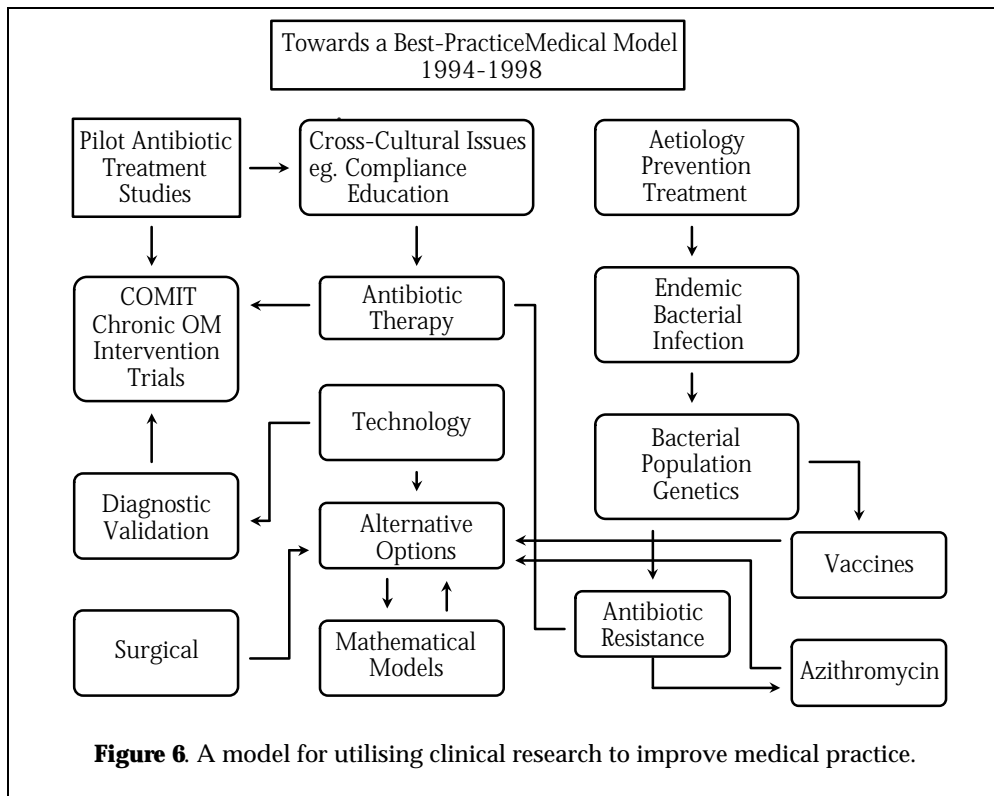
Leslie Yonovitz has presented seminars on the bioethical requirements for valid informed consent when indigenous Australians participate in "western" health care. She is also exploring the relationship between informed consent and adherence/ compliance.

Hearing Loss within the Justice System

Research shows that the prevalence of middle ear disease in Aboriginal people is at least ten times the rate found in the general population. Aboriginal and Torres Strait Islanders comprise 1.4 percent of the Australian population and an overall 14.6% of the national prison population. *The Northern Territory has the highest percentage of Aboriginal representation per State/Territory, with 70-80 percent of the prison population being Aboriginal.* The cycle of Aboriginal over-representation in custodial institutions begins in childhood, with Aboriginal juveniles estimated to comprise between 30 and 40 percent of juvenile detention centre residents, while constituting only 1.8% of the national youth population. The various stages within the criminal justice system have particular communication demands. In addition, room (courtroom) acoustics often create an especially difficult listening environment. The effects of reverberation and background noise have been shown to have a differentially greater effect in hearing impaired listeners compared to normal hearing listeners. These effects are being studied by Sreedevi Aithal with respect to second language (non-native) perception, and the results suggest that much greater difficulty is experienced by Aboriginals listening to English compared to their first or native language. An important basis of justice and protecting these rights requires that defendants are able to understand and comprehend issues related to their own case. Communication with the court, their lawyers, and those in correctional facilities are essential to ensure that hearing-impaired defendants have equal access to our legal system. The need to identify *communication disability* and *disadvantage* for Aboriginal involvement with the criminal justice system is the first, essential step in addressing neglected needs of hearing-disabled Indigenous defendants and prisoners. It is clear that many Aboriginals in custody require support, including medical services and audiologic intervention in all aspects of their interactions with police, judicial, correctional and rehabilitative services. This research is supported by the Criminology Research Council.

Best-Practice Models in Medical and Habilitative Services

A description of best-practice models currently in place within the Ear Health and Education Unit illustrating the synergistic relationship between medical and habilitative treatment is shown below (**Figures 6 & 7**). Equally important is the relationship between ear health and more effective education and greater employment opportunities.



Guidelines for OM for Indigenous Australians

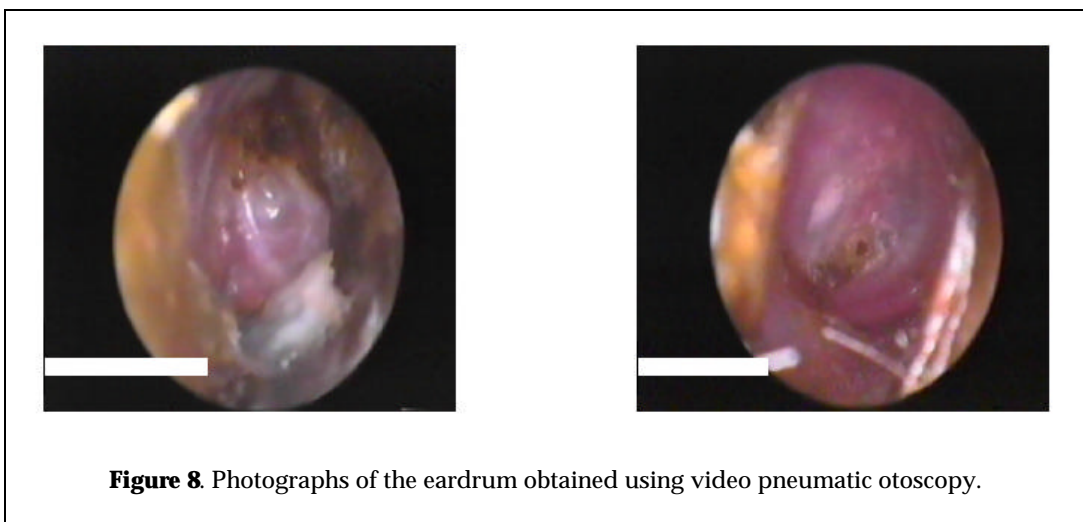
Guidelines on the prevention and control of otitis media and its sequelae in Aboriginal children were published (MJA, v 164, 20 May, 1996). These guidelines present recommendations to clinicians that are based upon an analysis of the available evidence in epidemiological and clinical studies. The key objective of these guidelines is to apply existing knowledge and expertise in the prevention and control of otitis media in Aboriginal communities. The MSHR staff including Amanda Leach, Judith Boswell, Terry Nienhuys, John Mathews, Val Asche, Tania Shelby-James, Mark Mayo, Sue Hutton, Albert Foreman and Anne Lowell have been cited for their contributions to this important document. A detailed critical appraisal of these guidelines is included in Amanda Leach's PhD thesis. Further descriptions of the rationale for various medical treatment options and strategies are currently in press.

BIOMEDICAL ENGINEERING PROJECTS

Recent technological advances mean that many of the basic assumptions about the aetiology and management of ear disease can be re-examined in a more systematic manner.

Air Pressure Monitoring System with Video-Pneumatic Otoscopy

A specially designed instrument was constructed for the randomised controlled of early antibiotic therapy to prevent chronic otitis media. The purpose of the instrument is to provide real-time and recordable visualisation of pneumatic pressures used in video otoscopy. A white bar changes length in proportion to the applied pressure and is shown in the following figure. The instrument was designed by Al Yonovitz and constructed by Aaron Leach. It is the first visual display of pressure to be synchronised with video otoscopy. Diagnostic tapes have been edited for training and education of ear health workers. In addition a diagnostic verification study involving Australian ENT specialists with experience examining rural and remote Aboriginal children is currently underway. This could not be done without this innovation. This research is supported by the NHMRC.



Using Microprocessors for Compliance/Adherence Monitoring

Significant developments in low-cost miniaturisation of microprocessors complete with program and data memory have provided a rationale for applying these devices to compliance issues. The size of these devices are approximately 1 sq-cm, including the battery with a depth of approximately .5 cm. With very small power requirements, these devices can provide a reminder alert (tonal alarm twice each day) as well as an automated compliance time logging system. These computer devices have been mounted within plastic boxes that include press buttons, audible signalling alarms and connecting ports to a laptop computer. These devices can also be placed in the base of a medicine bottle and use a tipping sensor, or incorporated into a syringe tray with switch mechanisms that detect the removal of syringes at the time of treatment. A small lap-top computer is used to provide a file transfer of compliance data from the compliance monitor. The research was supported by Merck, Sharpe and Dohme.

Noise Level Monitor for Public Health Education

The Ear Health and Education Unit has annually participated in Deafness Awareness Week. This event provides a significant public service by providing ear health education as well as personal hearing screenings. A microprocessor based sound level meter was constructed that provided a measure of the sound intensity of environmental and industrial noise. The device displayed the sound intensity as a series of vertical large lights that were readily observed by groups of people. The device was part of a display that emphasised the importance of hearing conservation. The device will be used in schools and community service projects. The instrument was designed by Al Yonovitz and constructed by Aaron Leach and Patrick Scott.

OTHER COLLABORATIVE RESEARCH INITIATIVES

While well-designed research studies improve our understanding of disease and management options, improvements in health outcomes can only be achieved through effective implementation by the local health services.

Territory Health Services

Development of otologic and hearing evaluation guidelines

The MSHR and Ear Health and Education Unit have participated in the development of the Standard Protocols used by the Royal Darwin Hospital, the Child Health Policy Unit, and the Top End Standard Treatment Manual, and in the Coordinated Care Trials taking place in Katherine West and the Tiwi Islands. These standards incorporate a time table for diagnostic and intervention plans. More detailed descriptions of the rationale for various treatment options and strategies are currently in press.

Australian Hearing Services

In 1995, collaborative research between MSHR and the Australian Hearing Services (AHS) was formally launched with the signing of a Memorandum of Understanding. A number of projects have been undertaken, including best-practice service delivery in providing amplification systems for Indigenous Australian children. This project provides a system of intervention allowing an Educational Audiologist to liaise with schools, parents and AHS audiologists to optimise treatment for hearing abilities of primary and secondary aged school children. Additionally, a project has been funded to

provide epidemiological data and guidelines concerning hearing disability in Aboriginal prisoners. This project includes acoustic analysis of criminal justice spaces that could exacerbate hearing disabilities in defendants. The aim is to safeguard the rights of those accused of crimes and provide a fairer system of justice for all Australians.

World Health Organization

The MSHR has presented its research and training program in ear disease to the World Health Organization. The establishment of an *Australian WHO Collaborating Centre for the Prevention of Hearing Impairment* in Darwin will allow the MSHR to become part of an international network carrying out activities consistent with WHO priorities. This would hopefully improve dissemination of clinical and research results that address the needs of disadvantaged populations throughout the world. The program is in the final stages of approval.

FUTURE DIRECTIONS AND SUMMARY

The Ear Health and Education Unit has developed its program of research, service and training to address the specific lifetime needs of high risk populations. Prevention is the highest priority for reducing ear disease, and any interventions must be considered in the context of other health issues affecting the individual and the community. Our mission is to employ models of systematic research that will be immediately beneficial, as well as projects that require longer-term, multidisciplinary approaches to complex problems.

Our understanding of the disease process in Aboriginal children highlights opportunities for more effective intervention strategies. For example, the "vicious circle of inflammation" suggests that prevention of invasive respiratory disease in infants may be achieved through reducing bacterial loads in others. Pre-school children, in particular, suffer less invasive disease but are likely to be the major source of numerous bacterial transmissions. In addition, newly available pneumococcal vaccines have been designed in developed countries to provide protection for children at the age of highest rates of invasive disease (second 6 months of life). Unfortunately these vaccines are unlikely to prevent early infections in Aboriginal infants.

Great strides could be achieved through research that provides an evidence-based approach to medical, audiological, and educational interventions. The experience gained through our first RCT in rural and remote Aboriginal communities will hopefully be applied to other potential interventions *eg.* vaccine trials, URI and CSOM treatment, grommet insertion *etc.* Future evaluations will continue to acknowledge the importance of community attitudes and health beliefs, the principles of community control, and the necessity of self-determination. It is our belief that these efforts will lead to a significant and substantial improvement in the health of Aboriginal Australians.

Health Social Sciences Unit

Peter d'Abbs

At the beginning of 1997, a new Health Social Sciences Unit was created at the School, incorporating the former Substance Abuse Unit. This move signalled the School's growing involvement in research related to social and cultural aspects of health issues and health interventions, alongside the biomedical aspects already addressed by other research programs at the School. The new Unit will also build on work carried out by the Central Australian Unit, which has an established and continuing commitment to research on economic, social and cultural issues related to health. Establishment of the Cooperative Research Centre for Tropical and Aboriginal Health in July 1997 has provided further opportunities for the School to develop strategic links with other bodies, including governmental and Aboriginal controlled service organisations, and with them to foster a more extensive research program in fields such as the delivery of health services, social and cultural aspects of cross-cultural clinical encounters, and the managerial needs of remote, community controlled health services. Some initial steps in these directions are outlined below.

Over the past five years, research activities have focused on four main areas, namely :

- the relationship between alcohol misuse and violence, and policies to reduce alcohol-related violence;*
- planning for, and evaluation of, community-based public health initiatives to reduce alcohol-related harm;*
- policies to minimise the harmful effects of drinking kava (a recreational drug imported from the Pacific Islands into a number of coastal Arnhem Land communities); and*
- evaluation of cross-cultural health services.*

In addition, a number of postgraduate students have commenced research theses, and staff members of the Unit have contributed to developing and running units in the Masters in Public Health Program conducted by the School on behalf of the University of Sydney and Northern Territory University.

ALCOHOL MISUSE AND VIOLENCE

In 1993 the Commonwealth Department of Human Services and Health (as it was then known) commissioned a number of research projects to examine the relationship between alcohol and violence, as a lead-up to a major symposium aimed at developing new policy directions. The Unit competed successfully for one of these consultancies, to conduct a review of alcohol-related violence among Aboriginal and Torres Strait Islander communities. A multi-disciplinary team brought together for the project included experts from the Peninsula and Torres Strait Regional Health Authority, Cairns, and James Cook University of North Queensland, as well as the Unit's own resources. The resulting report, entitled *Alcohol-Related Violence in Aboriginal and Torres Strait Islander Communities*, drew together, in a way not previously attempted, the various theories, perspectives and controversies associated with the topic, and charted areas for future policy initiatives.

In the meantime, alcohol-related violence had become an immediate policy issue closer to home. In July 1993 the Unit was invited to undertake a review of Darwin nightclubs and problems associated with them, and to make recommendations to minimise problems. The review was precipitated by the issue of trading hours, but the research design adopted was based on existing research which demonstrated that the effects of trading hours could not be isolated from other factors, such as patrons' expectations and other attributes, management practices, the nature and scale of policing, and the availability of transport away from venues.

The research was conducted by a team led by Peter d'Abbs, involving Peter Thomsen who, as well as being a current member of the School's Aboriginal Policy and Health Education Unit, had also worked in the past as a nightclub 'bouncer', and John Forner. The study drew on a variety of sources of data, including police statistics relating to violence and disorder, direct observations in and around the venues, interviews not only with licensees and their staff, but also with regular nightclub-goers, and examination of documentary sources [135].

One of the more novel parts of the research involved voluntary Blood Alcohol Level testing of people in the vicinity of nightclubs. Concerns that nightclub patrons might find the testing intrusive quickly evaporated when it became apparent that almost all of those in the street welcomed the opportunity to find out how much their drinking had affected their Blood Alcohol Levels.

Testing was conducted between 2.00 am and 4.00 am on a Saturday morning, and again between 4.30 am and 6.30 am. Tests were only conducted if at least 10 minutes had elapsed since the participant's last alcoholic drink. Participants were not asked to give their names or any other personal details. A total of 154 people were tested, 100 of them male. Only 8 of the 154 were tourists or visitors to Darwin.

Among both men and women, levels tended to be markedly higher after 4 am, although the maximum levels recorded did not change significantly. Among women, the major change was in the proportion recording a BAL between 0.08 and 0.15; this rose from 17% of women tested before 4 am to 42% of women tested after 4 am. Amongst males, the main increase was in the proportion of people who were over 0.15 : 20% of those tested before 4 am, and 38% of those tested after 4 am.

The findings, in short, demonstrated that levels of intoxication in the vicinity of nightclubs were high, and appeared to be related to trading hours. In itself, however, this finding did not provide a basis for policy recommendations, since a number of studies have shown that intoxication *per se* is not a sufficient explanation for alcohol-related violence. In the case of licensed premises, a crucial factor is the way in which intoxication is managed.

In order to find out more about this factor, the research team spent some 91 hours observing on licensed premises, during which time they recorded 33 incidents, 27 of which involved physical violence. The single most common precipitating event in the observed incidents of violence was conflict between patrons and security staff connected with ejection, entry or attempted re-entry. The second most common precipitating event consisted of challenges to fight, issued by one party to another, apparently unprovoked assaults, and assaults apparently associated with 'pay-backs'. Once again, intoxication appeared to play an important 'lubricating' role in these incidents, but the incidents also testified to the presence, among at least some patrons, of a drinking culture in which fighting was a more or less acceptable component.

A third factor that emerged from the incidents was the inadequacy of available transport away from the nightclubs at closing time. The dearth of taxis and absence of buses led to quite large numbers of more or less intoxicated people standing around, becoming frustrated and, often, aggressive.

In sum, the prevalence of violence and disorder appeared to be a function of (a) high levels of intoxication, (b) situational factors, such as low levels of training among bar and security staff, and inadequate transportation facilities, and (c) a 'drinking culture' that condoned fighting.

Several, although not all, of the review's recommendations were subsequently adopted by the Northern Territory Liquor Commission, initially on a three-month trial basis. These included greater emphasis on training staff in responsible serving practices, a cover charge for admission after midnight, and a reduction in trading hours associated with closure at 4.00 am instead of the previous 6 am. A subsequent evaluation, also carried out by the School, found that the reforms contributed to a fall in disturbances, property damage and other indicators of disorder, but not in the number of assaults. This, it was argued in the evaluation, was because although the reforms had modified some of the *situational* factors conducive to violence, other issues, such as lack of training and regulation of security staff, had remained unaddressed [209].

COMMUNITY-BASED PUBLIC HEALTH INITIATIVES TO REDUCE ALCOHOL-RELATED HARM

One of the most notable features of recent attempts to reduce alcohol problems, especially in regional towns, has been the adoption by a number of communities of restrictions on alcohol availability. The towns of Tennant Creek in the NT, Derby and Halls Creek in Western Australia, and Aboriginal communities occupying the extensive Pitjantjatjara, Yankunytjatjara and Ngaanyatjarra lands that extend across portions of the NT, South Australia and Western Australia, have all been involved in placing liquor licensing restrictions on local outlets in order to reduce alcohol-related problems. Some of these restrictions take the form of informal agreements between licensees and community groups, while others have involved liquor licensing authorities.

The Unit has been involved in evaluating several of these initiatives.

In 1995, following the imposition of a six-month trial of restrictions in Tennant Creek, the Unit was engaged to work in cooperation with the NT Government's Living With Alcohol Program to evaluate the impact of the restrictions. The evaluation was conducted by Peter d'Abbs and Samantha Togni of the Unit, together with Ian Crundall of the Territory Health Service Living With Alcohol Program [273].

The trial measures were arranged in two phases, with each phase occupying 13 weeks. Both phases consisted of four main types of restrictions, namely :

- A set of special restrictions applying to Thursday trading;
- Conditions applicable to trading on days other than Thursdays;
- Additional restrictions applicable to front bar sales, and
- Additional restrictions applicable to takeaway sales.

The main distinction between phases 1 and 2 was that, in the former, restrictions on Thursday trading were more comprehensive.

The evaluation was designed to gather data both on *processes and events* associated with the trial, and on *outcomes* attributable to the trial measures. Outcome indicators were grouped under three major headings :

- Problems associated with public order, such as public drunkenness and alcohol-related crimes;
- Problems associated with health and welfare, such as the prevalence of alcohol-related injuries and illnesses, expenditure on food, and nutritional standards among children;
- Problems (and outcomes) associated with economic activities, including liquor sales, absenteeism and possible impact on other commercial activities.

During Phase 1 of the trial, the total prevalence of selected offences (assault, criminal damage, unlawful entry, stealing, interfering with motor vehicle) was 14.5% lower than in the same 13-week period of 1994.

Also during Phase 1 of the trial, the number of presentations at the Accident and Emergency Section of Tennant Creek Hospital in which alcohol was coded as a feature was 34% lower than during the same period in 1994. The number of presentations in which 'assault' was coded as a feature was 21% lower, and the total number in five diagnostic categories - namely, fractures, head injuries, injuries, laceration, and stab injuries - was 26% lower. The reductions were particularly marked among Aboriginal women.

In general, outcomes during Phase 2 of the trial were less marked than during Phase 1.

A community survey, conducted towards the end of the trial period, using a random sample of 270 people (200 from private dwellings, 70 from town camps), found that 58% of those interviewed were in favour of the trial measures, 21% were against them and 16% had mixed views. A majority of both Aboriginal and non-Aboriginal residents supported the measures.

A report of the evaluation was formally tabled at a Liquor Commission hearing, convened on 3 March 1996, to assess the impact of the trial measures and to determine future licensing conditions. Largely on the basis of the findings of the evaluation, the Commission subsequently announced that many of the restrictions would remain in place indefinitely.

In 1997 the Unit received a grant from the Western Australian Alcohol and Drug Authority to evaluate another six month trial of liquor licensing restrictions, this time in Derby, WA. The licensing restrictions were initially imposed by the WA Liquor Licensing Division in January 1997. Following an appeal against the restrictions by Woolworths, the restrictions were overturned. However, the licensees (including Woolworths) subsequently agreed to maintain the restrictions on a voluntary basis for the remainder of the six month trial period, and await the outcome of the evaluation before deciding on a future course of action [397].

Like similar initiatives elsewhere, the Derby initiative raises questions of broader significance, relating to the role of community-based groups in addressing health problems. Another study carried out by the Unit addressed this question more directly. In August 1995 the Unit was commissioned by the Kakadu/West Arnhem Gunbang Action Group to prepare a strategy for use by communities in the region to reduce alcohol-related harm ('gunbang' being the Gunwinggu term for 'alcohol'). The project involved four main elements :

- Gauging patterns of alcohol consumption and alcohol-related problems in the region;
- Identifying services and programs currently in place, assessing the extent to which these were being used, and identifying outstanding gaps in service provision;
- Consulting widely with groups in the region about their concerns and ideas, and
- Outlining a strategy for dealing with problems identified.

The West Arnhem region, as defined in the research brief, corresponds roughly with the catchments of the East, South and West Alligator rivers, and is the area occupied by those people who have been most directly affected by large scale uranium mining since the 1970s. It includes the mining town of Jabiru, the Aboriginal community of Oenpelli, and a number of smaller settlements. Total population is about 3,000, of whom about half are Aboriginal.

The project drew on five main sources of data: review of relevant literature; interviews with key informants; group discussions; official statistics relating to liquor sales, police offences and alcohol-related presentations at health clinics, and NT Liquor Commission files [272].

The study found evidence of extremely high levels of alcohol consumption, especially in association with two licensed clubs in the region. The study also reported that one of the clubs, through its control of a high annual turnover, had become a dominant economic and political institution in the community, with a result that non-drinkers were effectively disenfranchised. The report made a number of recommendations aimed not only at reducing consumption levels but also at making licensed clubs more accountable to their communities and at giving non-drinkers a say in club affairs.

The study also recommended steps to overcome gaps in current service provision. In particular, while the region was found to be served by primary prevention measures such as educational programs and residential *tertiary* treatment centres, virtually no programs existed at the level of *secondary* prevention, or early intervention. The report recommended the setting up of screening and early intervention programs at the two local community health centres.

The report of the study was formally adopted by the Gunbang Action Group in May 1996, and in December of that year the Group released for public comment a draft corporate plan, based on the report's recommendations.

More recently, the Unit was awarded a consultancy by the Commonwealth Department of Health and Family Services to examine the impact of alcohol restrictions placed in 1996 on Curtin Springs Roadside Inn, a tourist facility located on the Lasseter Highway that connects Alice Springs with Uluru and Ayers Rock Resort. The restrictions were introduced at the request of an Aboriginal women's organisation, the Ngaanyatjarra Pitjantjatjara Yankunytjatjara (NPY) Women's Council, which represents women throughout the Pitjantjatjara, Ngaanyatjarra and Yankunytjatjara lands of central Australia. At the time of writing this report, this evaluation was nearing completion.

In future, we plan to build on the individual studies conducted to date, to identify factors conducive to generating widespread local support, and achieving outcomes, on the one hand, as well as factors that impede local support and outcomes.

KAVA

In 1993 the School, on behalf of Territory Health Services, conducted a review of measures adopted three years earlier by the Northern Territory Government to control the sale and supply of kava, a psychoactive substance prepared from the crushed root of the plant *Piper methysticum* [70]. Although long used throughout the Pacific Islands for both ritualistic and secular recreational purposes, and in Australia by resident Pacific Islanders, it is only since 1981 that it has been used regularly among Australian Aboriginal communities, and even since that time its use has been confined to a handful of coastal Arnhem Land communities.

Ever since 1981, the consumption and alleged effects of kava have been a source of controversy, with many health professionals and others raising concerns about medical, social and other consequences of the very high consumption levels common in some communities. A study conducted by the School in 1988 by Professor John Mathews and his colleagues appeared to confirm many of these concerns, and helped to set the scene for the introduction of more regulatory policies.

The 1993 review found, however, that the measures introduced by the government had failed to achieve the three objectives ascribed to them, namely :

- to reduce per capita levels of kava consumption;
- to reduce the incidence of kava-related health, social and economic problems; and
- to establish mechanisms for regulating the sale and supply of kava, with a view to eliminating excessive profiteering from kava sales, and ensuring that, as far as possible, those profits that did accrue from kava sales were used for the benefit of kava-using communities, rather than for private gain.

The imposition of controls was found to have led to a fall in sales, but only in the short term. By October 1992, sales had reached a similar level to that prevailing prior to the controls being introduced.

The main reason for this result was the failure of the attempt to establish an orderly, regulated retail system under the control of community councils. This outcome could in turn be traced to three factors. Firstly, the conditions imposed on councils wishing to sell

kava were experienced as onerous bureaucratic requirements, that served no apparent purpose and merely added to the difficulties of organisations already struggling to discharge a broad range of functions and responsibilities. Secondly, with a few exceptions, the government had failed either to help councils fulfil the conditions attached to retail licences, or to enforce compliance. Thirdly, given these circumstances, it was not long before Aboriginal and other entrepreneurs realised that, with a few re-adjustments to take account of changed conditions, they could go on buying and selling kava almost as freely as before the controls were introduced.

Subsequently, the development of a clear policy on kava use was impeded by uncertainty as to the jurisdictional responsibilities of Commonwealth and Territory agencies.

In 1997 the Northern Territory Government once again turned to the School for policy-related research on kava, this time through the Sessional Committee on use and Abuse of Alcohol by the Community, which engaged the School in a consultancy to report on current patterns of kava use, and policy options for the reduction of kava-related problems [327].

EVALUATION

Part of the Unit's agenda for the future is to contribute to the development of culturally-appropriate models for evaluating policies and programs related to Aboriginal health. The evaluation projects outlined above have all been in the domain of alcohol or kava policy. More recently, however, the Unit has also been involved in the broader field of health service program evaluation. Late in 1997, the Unit was engaged by Territory Health Services to prepare an evaluation plan for an innovatory program known as the Katherine West Region Coordinated Care Trial (CCT). The CCT program is an offshoot of a national initiative designed to provide more responsive, efficient and effective services for clients with chronic conditions or who rely upon multiple services. The national, or mainstream, program involves pooling the various funds utilised to provide these services in selected trial sites, and establishing 'care coordinators' to administer the coordinated services.

The Aboriginal and Torres Strait Islander CCT program differs from the mainstream program in three important respects: firstly, it emphasises population based preventative measures rather than programs based on individual patients (although these continue to constitute an important element of the services); secondly, it embodies a commitment to indigenous control of the services concerned, and thirdly, it provides for additional funding in the form of 'cashed out' MBS/PBS benefits, set at the average national per capita level. This last element has been introduced as a response to the fact that most remote area health agencies serving indigenous Australians do not have access to MBS/PBS benefits because the services are not administered by medical practitioners or pharmacists respectively. An important source of health funds available to other Australians is therefore denied to remote Aboriginal people and organisations.

The Katherine West Region CCT is one of two earmarked for the Northern Territory (and one of four nationally), the other NT trial being located in the Tiwi Islands.

The evaluation plan prepared by the Unit for the consultancy became the basis for a separate tendering process to conduct the evaluation of the trial itself. The School's submission was successful, and, in July 1998, a research team under the direction of Dr Peter d'Abbs commenced the evaluation

LINKS WITH THE COOPERATIVE RESEARCH CENTRE

As mentioned earlier, the inauguration in July 1997 of the CRC for Aboriginal and Tropical Health has created new opportunities for intersectoral research into social aspects of indigenous health, with three of the five CRC program areas having a strong social orientation - namely, the Indigenous Education and Research Program, the Health Services Research Program, and the Public Health Research Program. In the first of these, the School late in 1997 appointed a Research Fellow, Dr Anne Lowell, to review published and unpublished literature relating to the relationship between health and education, and to conduct research in aspects of cross-cultural communication in classrooms and other settings related to education. A similar appointment - Mr Bob Boughton - has been made in Alice Springs.

The Unit was also involved late in 1997 in a workshop convened in Alice Springs under the Health Services Program of the CRC to develop a detailed research agenda for the program.

MPH PROGRAM

The Unit is involved in developing and teaching courses for the School's Master of Public Health Program, delivered on behalf of the University of Sydney and Northern Territory University. A new first year core unit - "*Sociology and Health : An Introduction*" and three elective units, two on substance abuse, and one on health program evaluation, have been introduced recently.

POSTGRADUATE RESEARCH STUDENTS

Ms Kath Kemp is engaged in doctoral research on cross-cultural issues in health services by studying the experiences of Aboriginal families in intensive care settings in hospitals. Dr David Thomas has commenced a doctoral study, examining the representation of Aboriginal people in medical research literature. Dr Rowena Ivers has commenced a PhD on smoking cessation among Aboriginal people. Dr Lam Tai Pong, a medical graduate of the University of Western Australia, is engaged in a doctoral study of the impact of land migration among traditional 'water people' in Hong Kong.

FUTURE DIRECTIONS

The future development and usefulness of social science research at the School will be a function of the extent to which we can, through innovative research designs and practices, foster three kinds of linkages: first with Aboriginal people, communities and organisations; second, with researchers in the biomedical domain, and third, with health service providers and managers. In all of these areas, much remains to be achieved, but in all of them, too, the School is uniquely placed to make a significant intellectual and practical contribution.

Molecular Genetics Unit

KS Sriprakash

This Unit engages in studies that: a) unravel the mechanisms of antigenic diversity in disease-causing bacteria; b) increase understanding of host-pathogen interactions; c) develop molecular methods to diagnose bacterial infection and to type otherwise non-typable strains; d) contribute to molecular epidemiology, and e) identify and characterise bacterial antigens that may be important as vaccine candidates.

STREPTOCOCCUS PYOGENES

Streptococcus pyogenes (group A streptococcus, GAS) can cause self-limiting infection or, if ineffectively treated, can lead to serious sequelae such as acute rheumatic fever (ARF) and acute glomerulonephritis (AGN). *S. pyogenes* also causes life-threatening invasive diseases like streptococcal toxic shock-like syndrome and necrotizing fasciitis. Penicillin still remains a very effective antibiotic against *S. pyogenes* infection. However, in severe systemic disease antibiotic treatment often may not resolve pathology, and the causative organisms are usually not recovered from ARF or AGN patients. Therefore, vaccines are being actively sought for protection against recurrent infections, toxic shock-like syndrome and other possible post-infection sequelae.

The Molecular Genetics Unit has been interested in GAS since 1989. By then, the detailed structure for streptococcal M protein, the major virulence factor responsible for conferring bacterial resistance to phagocytosis was established. M protein is highly variable at its amino terminus and type-specific antibodies are opsonic and protective.

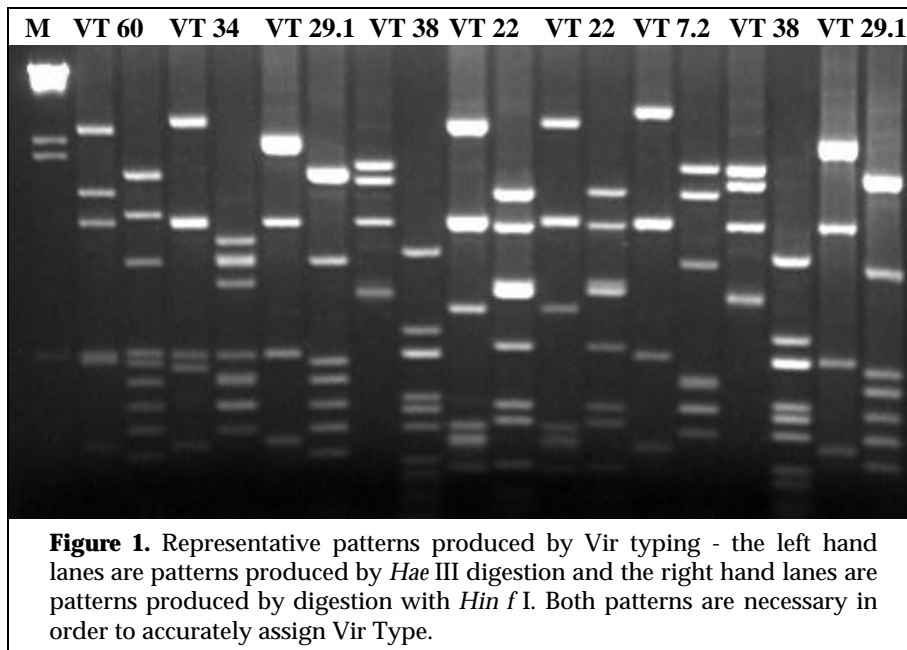
Although endemicity of streptococcal diseases in the Northern Territory of Australia (NT) were recognised by then, it was not until later that detailed epidemiological studies were undertaken by colleagues (from other Units) in this School. GAS epidemiology in Australia was recently reviewed [245].

Our initial aims were to determine the M-variants in the NT isolates and in the process unearth mechanisms of antigenic diversity. These studies were presented in the previous quinquennial report. In short, genes for M protein (*emm*) from many NT isolates were amplified by PCR and sequenced. The sequence data allowed us to group the *emms* into families. Ms Wendy Relf demonstrated the inadequacy of M serotyping for the NT streptococcal isolates [120] and this limitation was acutely felt in our epidemiological studies.

Novel Typing Method for GAS

"Necessity is the mother of invention" We reasoned that the *emm* locus may contain up to three *emm*-like genes flanked on each side by conserved regions. Upstream of the *emm*-like genes is a regulatory gene called *mga*; whereas downstream is the gene for C5a-peptidase, *scpA*. Amplification using PCR primers, targeting the conserved regions just

upstream of *mga* and within *scpA*, yields a highly polymorphic DNA fragment due to sequence and architectural diversity. This polymorphism can be determined by restriction fragment length analysis (RFLP) using *Hae*III and *Hin*fI. This molecular typing method is called Vir typing [164]. Vir typing is highly discriminatory, it is applicable to all isolates irrespective of their geographical origin, and produces patterns that are simple to interpret and can be performed within a day [353]. An example of vir typing is shown in **Figure 1**.



These characteristics have allowed us to conduct epidemiological studies. Among the 1991-1994 isolates from four communities of the Top End in the NT Mr Don Gardiner found 46 VTs (Vir types) [234]. Vir typing was also used to identify AGN-associated GAS in a widespread outbreak in 1995 [289]. Subsequently, Ms Megan Hibble found further VTs [287]. Collectively these studies showed that the reported per capita diversity of streptococcal isolates is the highest in the NT. Preliminary analysis suggests that different spectrum of VTs are found among the hospital isolates, in comparison with the community isolates. In collaboration with the Clinical Unit, we have further analysed VT distribution among invasive isolates and isolates from a ARF/rheumatic heart disease study (the details will be covered by that Unit).

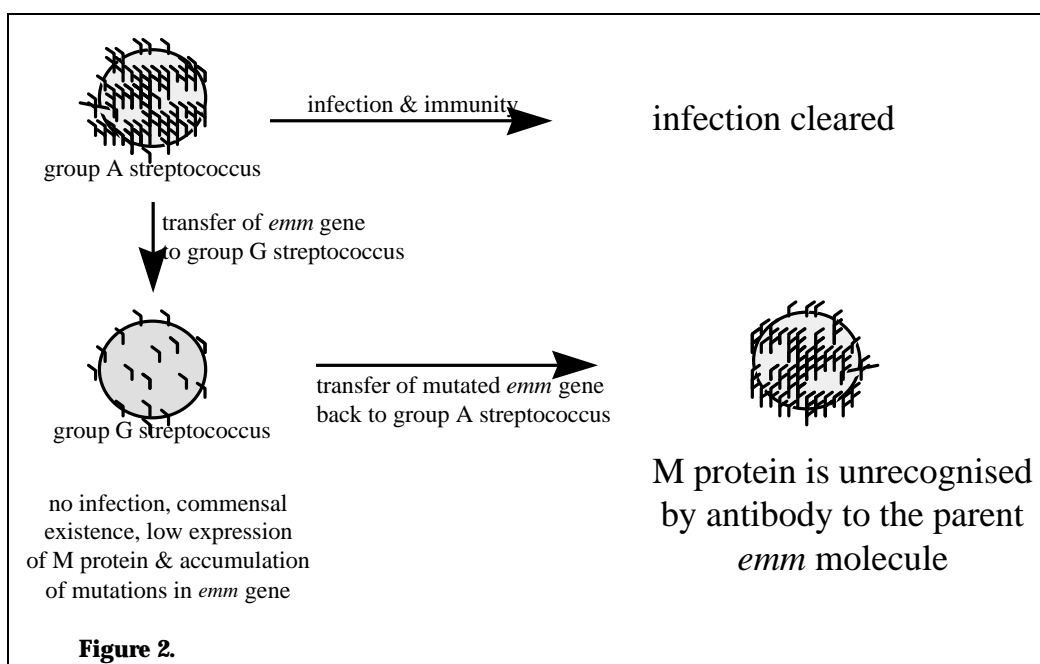
An important aspect of VT is that it scores diversity in the *emm*-locus. Thus the new information using Vir typing for isolates from a geographical region may correlate with M typing data previously collected. In fact we recently demonstrated this to be so for our isolates [348]. Vir typing is now being used in Diana Martin's laboratory in New Zealand. This technology is also being exported to laboratories in Thailand, India and Germany. A proposal was also sent to NIH as a recommendation for future typing of GAS isolates.

Mechanism of Antigenic Diversity of M Protein

Phylogenetic analysis of *emm* sequences has identified M proteins that are evolutionarily closely related to each other and has revealed frame-shift and compensatory frame-shift as a common mechanism of M protein diversity in GAS [120]. It has been realised for some time that although the incidence of ARF is high in the NT, throat isolation rate of *S.*

pyogenes is low. Moreover, earlier M typing results did not reveal frequent isolation rates for M5, M6, M18 or M24, which are historically ARF-associated types. One particular isolate, PL1, gave ambiguous serotyping results, sometimes typing as M5 and at other times as M non-typable. Upon sequencing, Mr Jon Hartas found that the *emm* sequence for PL1 is a close relative of *emm5*, showing frame-shift and compensatory frame-shift mutations. Thus, independently reconfirming the existence of this mechanism of antigenic diversity [168]. Further analysis using specific oligonucleotide probes revealed that although M5 is rarely present in the NT communities, there are many isolates which are close relatives of this M [168]. In the same study, a high rate of seroconversion among the Aboriginal population of the Top End in the NT to a semi-conserved region characteristic for M5-family was also observed.

As part of our validation of Vir typing for *S. pyogenes*, we tested the method on a range of other bacteria, including *Streptococcus* spp. Among them, human group G streptococci (GGS) gave a 1.5-1.8 kb PCR product, instead of a 4-7kb product normally associated with GAS [260]. Sequence analysis of the 1.5kb GGS product revealed a genetic mosaic upstream of the gene for C5a peptidase (*scpG*). This mosaic contained short evolutionary remnants of the *emm* gene, and upstream elements of its regulator, *mga*. However, all GGS have *emm* genes, but these are not linked to *scpG*. The genetic mosaic upstream of *scpG* suggests that lateral genetic transfer between groups A and G streptococci may have followed by genetic rearrangement. We believe that the donor for this lateral transfer might be a relative of GAS containing *emm1* [317]. To determine divergence of *emm* sequence types among our GGS isolates, we determined several *emmG* sequences. Of particular interest was the observation that a GGS isolate encoded an *emmG*, which is highly homologous to *emm* from a GAS isolate from the NT. This suggests that the lateral genetic transfers between these streptococci are ongoing [260]. This may provide another mechanism of antigenic diversity. Herd immunity to a GAS M variant may force the selection of new variants. While the new variants are being generated, the GAS with the parental gene may not be viable in the host. However, transfer of the gene to non-pathogenic GGS, which does not need *emm* for its commensal existence, provides a safe haven where the *emm* may accumulate mutations before it has an opportunity to re-enter GAS (**Figure 2**).



Molecular Genetics of *S. pyogenes*

During the course of the above work, we found that all group A streptococcal isolates irrespective of their geographical origin, had six rRNA (ribosomal RNA) operons. The spacers between the eubacterial small (15S) and large (23S) ribosomal RNAs, and the 23S and 5S rRNAs are generally variable and may be occupied by one or more tRNAs. As a consequence, a typing scheme based on RFLP analysis of the spacer regions, or the entire operon, was developed. A similar method was developed for non-typable *Haemophilus influenzae* at this school [197]. By contrast to many eubacteria, group A streptococcus show very little polymorphism in this region; only two *HaeIII* RFLP patterns were observed with more than 30 strains tested [316]. More interestingly, within a strain, all the six operons are of the same *HaeIII* RFLP type, suggesting a lack of allelic polymorphism in the rRNA operons. Since all the spacers in the operons are identical (and occupied by tRNA^{ala}), it may be possible to replace one or more of the operons with another sequence, via homologous recombination, thus providing a strategy for genetic studies.

To test this, Mr Jon Hartas and Ms Simone de Clouett constructed a plasmid vector, pFMKB, which can be used to insert into or replace a rRNA operon. We have demonstrated that it is possible to inactivate at least one of the operons without any deleterious effect on *in vitro* growth of *S. pyogenes* (manuscript in preparation). We will be using this vector to shuffle some of the streptococcal virulence genes into rRNA operon (see *Future Plans*).

***S. pyogenes* - Tissue Tropism and Primary Site of Infection for Invasive Diseases**

This work was undertaken in collaboration with Dr Debra Bessen at the Yale University School of Medicine, New Haven, Conn. USA. As mentioned before, there is architectural diversity of the *emm* locus among GAS isolates. This locus may contain one to three *emm*-like genes. As a result, five chromosomal patterns (A to E) as judged by PCR tests were recognised. Debra's work with northern hemisphere GAS isolates, largely from non-endemic regions, revealed that 96% of all throat isolates belong to patterns A to C, and 95% of skin isolates belong to either D or E patterns. An interpretation of these results is that the chromosomal patterns determine the tissue tropism for GAS. Ms Rebecca Katz from Debra's laboratory visited us last year. Rebecca and Megan showed that in the NT isolates the relationship between the chromosomal patterns and tissue tropism although apparent, is not as profound as those observed in Debra's study. This study was further expanded with Dr Bart Currie, Clinical Unit, to include invasive isolates. Whereas in Debra's study the seven invasive isolates tested were of A-C type, suggesting that throat is the primary site of infection for invasive streptococcal diseases, chromosomal pattern D was seen among our invasive isolates. Taken together, it may be argued that there is no correlation between the chromosomal patterns and the invasive disease, and that the primary focus of infection for streptococcal invasive disease depends upon the relative prevalence of skin and throat infection in a human population (manuscript in preparation).

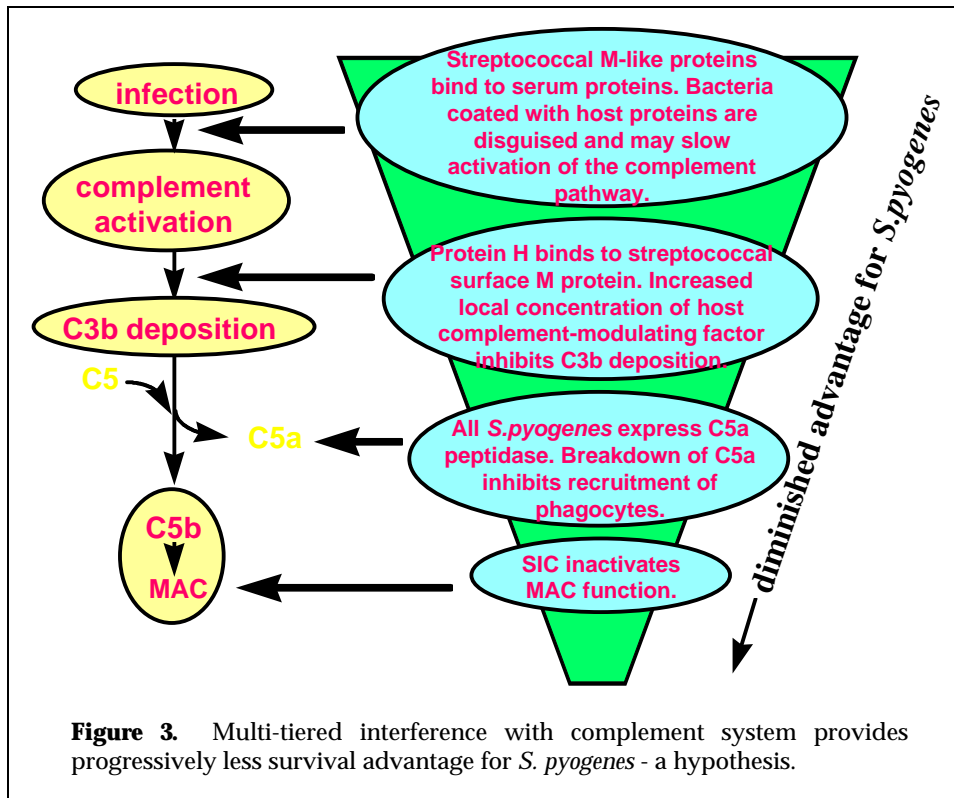
***S. pyogenes* and Chronic Renal Disease**

There is a controversy as to whether an episode of AGN progresses to more serious renal damage. In a study community (see Renal Unit report) with high incidence of chronic renal disease, we tested whether there was a relationship between exposure to

streptococcal M protein and proteinuria. Dr Alison Goodfellow together with Dr Hoy and Professor Mathews determined the presence of precipitating antibodies to streptococcal M proteins from sera of patients in Tiwi, NT. Modeling the large dataset, we found that the onset of proteinuria occurred at a younger age (30 years) in those people that were seropositive compared with seronegative (54 years). Together with Dr Hoy's observation that previous history of AGN predisposes to chronic renal disease, there is clear evidence that GAS have a role in chronic renal disease in this population.

Streptococcal Inhibitor of Complement (SIC)

In 1996, a Swedish group described a streptococcal extracellular protein which inhibits complement function. This protein, SIC, binds to clusterin and other blood proteins and also the membrane attack complex (MAC), the final complex of the complement cascade. SIC was only found in types M1 and M57 of the 55 M types tested. Both types 1 and 57 are nephritis-associated. SIC provides the fourth tier of streptococcal defence against host's complement mediated clearance of the pathogen (**Figure 3**). Because of this, and its restricted distribution we do not believe that SIC has an important role in the avoidance of host defence system [318]. But, it may have a role in AGN-pathogenesis. We have reasoned that in an AGN-endemic region such as the NT, these two types or their close relatives may be circulating in high proportion, or that strains other than M1 and M57 from the endemic region may express SIC or similar protein, or that both possibilities may exist. Seventy two strains representing about 95% of the NT isolates were screened for the SIC gene. Two types of the genes were found when compared with the original SIC gene - these were closely related to SIC (CRS) and distantly related to SIC (DRS). As in the Swedish study, among the NT isolates only *emm1* and *emm57* (genes expressing M1 and M57 respectively) or their phylogenetically closely related sequence types possessed CRS. However, the *emm12*- and *emm55*- containing strains possessed DRS, and this is also the case for M12 and M55 strains from the northern hemisphere. These latter M types are also AGN-associated. The CRS and DRS containing strains account for more than 6% of the NT isolates, which is a substantial representation. These studies have been communicated to *Microbial Pathogenesis*.



Seroconversion to Streptococcal Products

Two collaborative studies specifically to investigate human IgG to a streptococcal fibronectin binding protein (SFB I) and streptococcal exotoxin B (SPE B) were undertaken. Professor Singh Chhatwal from Braunschweig, Germany, characterised the SFB I which has a role in adhesion of the bacterium and invasion of GAS into epithelial cells. The gene for this protein is present in 70% of the strains. Alison and Megan have found that this is also the case for the NT isolates. Moreover, they found that most Aboriginal adults seroconverted to this protein as did some young children (manuscript in preparation). SFB I is highly immunogenic and a single infection is sufficient for seroconversion (Chhatwal, unpublished observations) These results were presented at the streptococcal workshop in Germany, arranged by Singh.

Almost all strains of GAS express exotoxin B (SPE B). Dr Jim Musser, Baylor College of Medicine, Houston, Texas, observed that higher titres of antibodies to this protein are found among the patients with less severe invasive disease than among the patients with more severe outcome. This inverse correlation may explain why, despite high endemicity of streptococcal infection, the incidence of severe invasive disease among the NT population is apparently low. Megan went to Jim's laboratory to initiate the work on the seroreactivity to SPE B. This work was later completed in Darwin. Again, almost all Aborigines living in the NT communities have seroconverted to this antigen (manuscript in preparation).

Funding

Funding from NHMRC, NHF, Channel 7 Children's Medical Research Foundation, Ramaciotti Foundation supported this research.

Future Directions

***S. pyogenes* vaccine studies**

Although not directly involved in group A streptococcal vaccine research, this Unit has made considerable progress towards intellectual discussions for the design of an effective vaccine for the endemic population. Using the VT information (see above) and sequence typing (ST) the representative VTs has allowed us to determine the proportion of major STs at a given time. Furthermore, it may be possible to group the STs into families of STs based on the sequence similarity at the sub-N terminal region. It may thus be possible to design minimal epitopes to be included in future subunit vaccines. Such studies are being planned by Alison in collaboration with Dr Bart Currie, Clinical Unit and Professor Michael Good at the Queensland Institute of Medical Research. National Heart Foundation has funded Alison's salary until the end of 1999 for this work.

The Unit will also collaborate with Dr Mark Walker, the University of Wollongong and Professor Singh Chhatwal, to investigate whether the SFB I and the streptococcal vitronectin binding protein offer protection against GAS colonisation in a mouse model. Funding for this is being sought from NHMRC this year.

Invasion-specific genes (ISGs) in S. pyogenes

Although *S. pyogenes* is regarded as a mucosal pathogen, this organism is also known to invade host cells and survive in the intracellular environment. It is reasonable to be expect that some genes are specifically turned on during the intracellular existence. Knowledge of the genes and their function is important if novel strategies to control invasive disease are to be developed. We have proposed the use of a reporter system based on the expression of green fluorescent protein and cell-sorting, to identify and characterise such genes. This proposal is a current submission to NHMRC.

Further work on SIC

How does DRS differ from CRS in biochemical properties? DRS and CRS have been recently cloned by Ms Sally Rosen of this unit, into pQE30. Additional clones containing fragments of CRS and DRS will be obtained. A structure-activity relationship study will be undertaken in collaboration with Dr Mark Wilson, a protein chemist at the University of Wollongong. This work has already commenced.

Dr Alison Goodfellow will test if CRS or DRS specific seroreaction correlates with AGN. Further long-term work will test if SIC is identical to the long recognised and yet poorly characterised Nephritis Strain Associated Protein (NSAP). Collaboration will be established to test if purified CRS or DRS cause glomerular changes in a mouse model (previously described by other workers). For this, isogenic sic⁺/sic⁻ strains will be created using our insertional vector. The sic gene will also be cloned into one of the ribosomal operons of sic⁻ strains in such a way that the gene is expressed from the strong rRNA promoter. All these constructs and their parents will be tested in the animal models.

Further work is under consideration to test whether SIC is deposited in affected kidneys. Kidney sections will be stained using SIC-antibodies. This work will be carried out in collaboration with Dr Wendy Hoy of the Renal Unit. Grant support for this will be sought.

Population genetics

The Unit will contribute to the population genetics of GAS being planned by Professor Mathews and Dr Don Gardiner in the School. We have already exported our molecular typing system to Thailand (Dr Pruksakorn), India (Professor Ganguli), Germany

(Professor Chhatwal) and New Zealand (Dr Martin). We will test whether there is an inverse correlation between the extent of *emm* diversity and human population density. This may be reasonable to expect if herd immunity indeed plays a part in selection against the M types to which the community has existing immunity.

CHLAMYDIA

Chlamydia trachomatis, an intracellular bacterial parasite, causes conjunctivitis, trachoma, non-gonococcal urethritis, pelvic inflammatory disease, lympho-granuloma venereum, and neonatal respiratory infections in humans. The prevalence and incidence of many of these diseases are high in the Northern Territory population. Therefore, the study of *C. trachomatis* is of global importance and relevant for the local epidemiology. Moreover, its unique life-cycle, obligate intracellular habitat and poorly understood pathogenic mechanisms in their own right provide interesting challenges.

Since the physical establishment of this School in 1985, the molecular genetics unit has been studying *C. trachomatis* with a view to a) use of chlamydial plasmid DNA sequence for DNA-based diagnosis of *C. trachomatis* infection; b) understand developmental regulation of genes and c) identify candidate-antigens alternative to the major outer membrane protein for potential vaccine antigens. A detailed study on the characterisation of the plasmid, its use in DNA-based diagnosis, and development of an *in vitro* transcription system to study gene regulation were described earlier (previous quinquennial reports). The progress from 1993 to 1998 is reported below.

Studies on Gene Regulation in Chlamydia

In 1993 we reported the development of a successful *in vitro* transcription system [44] in collaboration with Professor Tom Hatch at the University of Tennessee, Memphis, USA. Since our work prior to this (see previous Quinquennial Review document) suggested that there is no consensus among chlamydial promoter sequences, it was a logical progression to study specificity of sigma66 (*Escherichia coli* sigma70 homologue) by using the transcription system. Hence, numerous mutants of a previously recognised promoter were tested.

The choice of the promoter for this study is important. Firstly, it should be functional through out the life-cycle of Chlamydia. Secondly, it should be a strong promoter to permit detection in an *in vitro* assay. Finally, since the chlamydial and *E. coli* major sigma factors are highly homologous, for comparative studies it is advantageous if the chosen promoter has activity in *E. coli* transcription system. A plasmid promoter for a counter transcript, pCT, previously described by us fulfilled all three criteria.

Using polymerase chain reaction (PCR)-based saturation mutagenesis, Ms Sarah Mathews obtained a comprehensive set of mutations within the -10 and -35 boxes of the pCT promoter. These mutants were tested in an *in vitro* transcription assay using chlamydial extract and *E. coli* enzyme. The results [105] showed that the chlamydial sigma66, although requiring both the -10 and -35 boxes, could tolerate considerable variation in these boxes, whereas many of the mutants were inactive with *E. coli* RNA polymerase holoenzyme. This was a surprising result, given the extensive similarity in various domains in the sigma66 and sigma70. However, these results are consistent with an apparent lack of consensus in chlamydial promoters. Furthermore this suggests that other factors may modulate sigma66 recognition of chlamydial promoters.

For screening purposes the *in vitro* transcription assay used in the above study is tedious and cumbersome and a simpler assay is therefore necessary. A convenient reporter system for *in vitro* transcription was developed by us [106]. The reporter system is based upon specific and strong interaction between phage R17 coat protein and a specific 21 bases long RNA sequence (binding site). The novel template has the binding site placed downstream from a promoter. The transcription reaction can then be monitored by simply adding the coat protein to the product transcript (which will be radioactively labelled) followed by gel-retardation assay. The coat protein, the only special reagent required for this assay, can be easily prepared in bulk and stored for a long time at 4°C. Sarah demonstrated that this assay can be successfully used for *in vitro* transcription studies in Chlamydia.

During the course of these studies, we found that the chlamydial extract used for *in vitro* transcription had an endonuclease activity which created single stranded breaks (nicks) in DNA. More interestingly, the nicks were strand-specific and the enzyme (nickase) introduced nicks near the strong promoter (pCT) in the non-template strand and also exhibited sequence preference [107]. We believe that the nickase acts in concert with topoisomerases, chlamydial histone-like proteins and other early-stage-specific basic proteins (these proteins were described by other workers) to regulate DNA superstructure in elementary and reticulate bodies of Chlamydia.

Studies on Novel Surface Proteins

As mentioned previously, one of our research aims was to identify surface proteins that could be potential vaccine antigens. The chlamydial major outer membrane protein has been extensively studied as a possible candidate, but the results thus far are discouraging. Our initial attempts were centred around chlamydial ATP/ADP-translocase. This pathogen is incapable of making high energy compounds and needs to import nucleotide triphosphates from the host cells. Therefore, the translocase may fulfil a vital function for Chlamydia, and it is likely to be membrane associated. Attempts to clone this gene in late 1980s were not successful (Booth S and Sriprakash KS, unpublished observations). However, a clone which encodes a protein which is potentially membrane associated was isolated but the sequence had no match to entries in the extant nucleotide database. Further work was abandoned until 1994, when homology with a potential virulence factor from *Salmonella typhimurium* was found for the first time. By using bubble-PCR strategy, Mr Garry Myers extended the sequence information downstream from this hydrophobic protein. Three open reading frames were found. Principles of computational biology were applied to determine their structure and relationship to other similar proteins in the database. The results of this analysis revealed that the translation products of the three open reading frames are likely to be associated with chlamydial cell membrane or exported out of the cell, and hence are collectively referred to as **chlamydial m**embrane **a**ssociated **p**roteins (CMAP1, CMAP2 and CMAP3 respectively).

The CMAP1 gene or parts thereof, could not be cloned into an expression vector. A substantial part of CMAP2 and CMAP3 genes were cloned into pGEX vector. Using the CMAP1 peptides corresponding to regions of high immunogenic potential, Garry found that patients exposed to Chlamydia are seropositive to this protein. A correlation between the degree of exposure to chlamydial infection and the degree of anti-CMAP1 reactivity was also found.

Antibodies were raised in rabbits for partially purified recombinant proteins and the CMAP1 peptides. Using western blotting, Garry demonstrated expression of CMAP2, but CMAP1 and CMAP3 were not detected. The 25kDa CMAP3 is highly homologous to a 76kDa *C. pneumoniae* antigen which was shown to inhibit chlamydial infection using an *in vitro* protection assay. By rtPCR (reverse transcriptase-PCR), a transcript corresponding to CMAP3 was detected. However, to-date there is no evidence to indicate the presence of the protein in *C. trachomatis*. Garry recently submitted this work for his PhD degree.

Mr Richard Grinvalds is continuing this work. He is examining whether antibodies to any of the three CMAPs neutralise chlamydial infection of cell cultures. Preliminary results suggest that CMAP2-antibody does not protect against infection of cell culture. Unfortunately, most of the assays are semi quantitative. Recently, an assay for glycogen detection in clinical specimens of *C. trachomatis* was described in the literature and Richard has successfully adopted this to quantitate the degree of *C. trachomatis* infection in HEp2 cells. This assay is being used in neutralisation studies.

Funding

Chlamydia research at the Unit was undertaken with grants from ARC, NHMRC, Channel 7 children's Medical Research Foundation and School's internal sources.

Future Directions

Tryptophan and latency

Chlamydia is often associated with latent infection in humans. Experimental latency can be induced *in vitro* by gamma-interferon treatment which reduces intracellular tryptophan pool, or by starvation for tryptophan. We believe that CMAP3, a tryptophan-rich protein, is a sensor for the level of intracellular tryptophan. Once, the intracellular available pool of tryptophan plunges to an unacceptable level, synthesis of CMAP3 consumes the remaining tryptophan quickly and diverts the life cycle to latency. To test this hypothesis, the effect of varying concentration of tryptophan will be studied on the synthesis of CMAP3.

Cellular location of CMAP1 and CMAP2: The antibodies raised against these proteins will be used to determine the cellular location of these proteins by means of electron microscopy. Facility for this is available at the NTU.

Transformation system

We will attempt to obtain funding to develop a transformation system for Chlamydia. As the genome has been almost completely sequenced, it is timely to design gene knock-out experiments. The vector will be based on the chlamydial plasmid.

Nickase characterisation

Funds will be sought from ARC to study the specificity of the chlamydial nickase, its role in transcription control and its developmental regulation.

OTHER CONTRIBUTIONS

The Unit has contributed to studies on a) population dynamics of variants of non-typable. *Haemophilus influenzae* infection in an Aboriginal community, b) molecular

biology and molecular diagnosis of *Calymmatobacterium granulomatis*. Details of these studies will be presented elsewhere in this report.

ACKNOWLEDGMENTS

During the past four and a half years Ms Liz Wilson has provided excellent technical support to various projects. I thank her for this. I also thank members of the Microbiology Department of Royal Darwin Hospital for sending us GAS strains.



Molecular Parasitology Unit

David J Kemp

The aim of the Unit is to use modern molecular methods to answer questions that are important in the health problems of our region but cannot be answered by older approaches. We collaborate with several other Units as well as with colleagues from Territory Health Services and work in cooperation with communities in order to achieve this. Our work on Haemophilus influenzae in collaboration with the Ear Unit and Professor Mathews has led to a new perspective on its epidemiology. Our work with the clinical unit on scabies has provided the first ever molecular data on this parasite and shown that there are distinct populations on dogs and people, an important consideration for control measures. Our work on donovanosis, in collaboration with Dr Frank Bowden of Territory Health Services, has led to a non-invasive diagnostic test by PCR, the first major advance in this field since 1905. Our work on malaria has identified a new gene family which we have called clag which is vital to cytoadherence. It may well have wider importance in cellular interactions around the lifecycle of the parasite and provide a multistage target for new chemotherapeutic agents. All of these projects provide solid frameworks for future work.

MALARIA

Identification of *clag*, a Gene Required for Cytoadherence

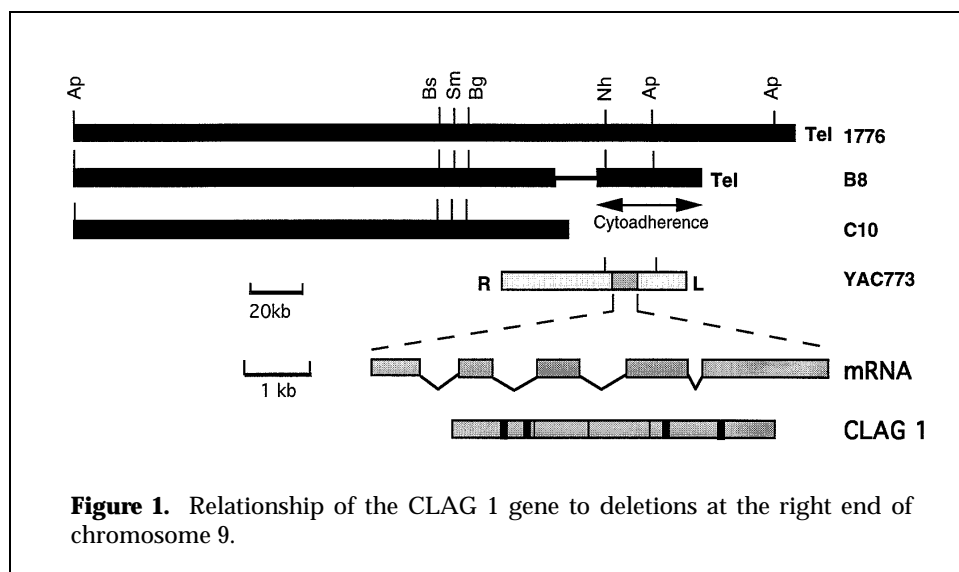
Plasmodium falciparum modifies the surface of host erythrocytes, producing structures termed "knobs" and expressing polypeptides that serve as ligands for endothelial cell receptors. The resulting cytoadherence interactions in the microvasculature can mediate severe pathology in various organs including cerebral malaria. Cytoadherence is currently a major area of malaria research as a better understanding of its mechanism may lead to the development of drugs or vaccines. It is generally believed that cytoadherence and invasion of red blood cells are the two most promising points of attacking the parasite.

Products of individual members of the *var* multigene family, collectively known as PfEMP1, together with the knob-associated histidine-rich protein (KAHRP) are essential components in these interactions. The role of KAHRP was first recognised because of subtelomeric deletions of its gene on chromosome 2 that render the cells knobless.

Other as yet undefined gene products are also essential. For example, during *in vitro* cultivation isolates of *P. falciparum* commonly undergo loss of cytoadherence, as measured by binding to C32 melanoma cells. We have associated this loss with subtelomeric deletions of chromosome 9. Independent deletion breakpoints are tightly clustered and selection by binding a mixed population of parasitised cells to melanoma

cells results in co-selection of the undeleted form of chromosome 9 in lines tested. We proposed that a gene essential for cytoadherence must be located in this region. As there are no *var* genes in this region in cytoadherent clones such as ItG2 this is a novel gene. The product of such a gene may associate with the PfEMP1-KAHRP complex or may be an independent component at the surface of the red cell. Alternatively it may be necessary for transport, processing of or regulation of *var* expression as PfEMP1 was not detectable on the surface of most cells bearing deletions.

Work of Deby Holt, Peter Bourke and Colin Sutherland over the past five years (supported by the Wellcome Trust) resulted in a detailed map of the region (**Figure 1**) [217, 218, 231, 355]. We have amplified by long PCR segments totaling the entire 55kb containing this cytoadherence locus and sequenced about half of it; the rest will be done at the Sanger Centre, UK as part of the malaria genome sequencing project.



In May 1997 sequencing revealed a prime candidate gene and since this time our group consisting of Katharine Trenholme, Don Gardiner, Deby Holt, Liz Thomas and Mark Mayo have made enormous progress. The gene is located just distal to the common breakpoint, encodes at least five exons within a region of at least 7 kb and is expressed in blood stages; it has been termed the cytoadherence-linked asexual gene (*clag*). Most importantly, a hydrophobicity plot predicts four transmembrane domains in the protein CLAG, in accord with a role for the corresponding protein CLAG at the red cell surface.

We have transfected an antisense construct of *clag* in vector HC 1 into stably cytoadherent *P. falciparum* clone 3D7. The resulting pyrimethamine-resistant line showed 10-20 fold lower binding to melanoma cells and to purified CD36 than did 3D7, consistent with the hypothesis that *clag* is essential for cytoadherence [349]. We have transfected a construct of *clag 1* in vector pTgD-TS.C5/H3 into 3D7 and this has now integrated into chromosome 9 by homologous recombination. The resulting line showed 10 fold less binding than did 3D7. Currently we have cloned the line bearing this targeted gene disruption of *clag* and confirmed the result.

Clag is Not Alone : The *clag* Gene Family

Recently we discovered in data from the malaria genome sequencing project a number of sequences closely related to *clag* on other *P. falciparum* chromosomes and hence *clag* is a

member of a gene family. As the *clag* targeted gene disruption did not retain the ability to cytoadhere to CD36 we infer that these related sequences are not homologues that carry out the same function as *clag*. This suggests that they are paralogues with related functions. We therefore propose the following hypotheses:

1. **The *clag* gene family is essential to cytoadherence, with different paralogues involved in binding to different receptors**, or alternatively :
2. **Paralogues of the *clag* gene family are important in cellular adhesion interactions at different stages of the lifecycle.**

We wish to examine these hypotheses and distinguish between them by analysing the structure, stage-specific expression, function as revealed by TGD and if relevant, cytoadherence binding specificity of a number of members of the *clag* family. In the longer term this could provide information critical to control of severe malaria and it is quite possible that some members may encode candidate vaccine molecules. It is also quite possible that they could be key targets for new chemotherapeutics that function at multiple points of the life cycle.

Future Directions

We wish to understand two major aspects. First, we wish to know the detailed structure, function, location and role in binding of CLAG itself. Second, we wish to know what functions the other members of this family of genes might have.

We propose to use the new malaria transfection technology with standard molecular and cellular approaches to examine the following questions about *clag*. Is PfEMP1 present on the surface of *clag 1* knockouts and if not, is its mRNA present? Can chromosome 9 deletion strains be complemented by *clag 1* alone? Is CLAG 1 located in the red cell membrane and if so, is it associated with the knob complex? Does CLAG 1 interact with the PfEMP1-KAHRP complex? Does CLAG 1 allow binding via PfEMP1, or is it an "undiscovered parasite adhesin"? Which endothelial receptors interact with CLAG 1? Which regions of CLAG 1 mediate functions uncovered above? Does isolate-specific sequence diversity suggest a role for CLAG 1 in natural immunity? Do antibodies inhibit binding to melanoma cells, CD36 or other known endothelial receptors? Do expressed segments of CLAG 1 inhibit binding to melanoma cells or endothelial receptors?

We will address a number of general questions to members of the *clag* gene family. For example, how many other members of the *clag* gene family are there? Is expression of the *clag* gene family restricted to blood stages or are some or all of them expressed at other stages? Do other genes of the *clag* family function in cytoadherence and if so, is this function restricted with respect to receptors? What are the cellular locations of proteins of the CLAG family? Are genes of the *clag* family subject to switching in a similar sense to those of the *var* family? What is the phenotype of each *clag* paralogue knockout as revealed by growth in *Anopheles*? Are proteins of the CLAG family potential vaccine candidates? Could proteins of the CLAG family have potential in the prevention or reversal of severe malaria?

Funding

We have applied for funding from the NHMRC to support the project on *clag* itself, and from the NIH to support studies on the *clag* family.

This work was supported by the NHMRC, the Wellcome Trust (UK) and the Howard Hughes Medical Institute (USA).

SCABIES

Are *Sarcoptes scabiei* Mites on Humans and Dogs in Aboriginal Communities the Same or Different Populations?

Scabies ("itch mite") is a parasitic infestation of the skin by the mite *Sarcoptes scabiei*. Scabies is a major problem among children in many Aboriginal communities in Australia, often complicated by streptococcal infections. It has been difficult to study the epidemiology of scabies as there have been no biochemical or morphological markers.

Shelley Walton developed a DNA fingerprinting system using 3 independent microsatellites that is the first marker system to discriminate between individual *S. scabiei* mites [324]. In collaboration with Bart Currie we have used this to examine some important basics of epidemiology that has not been possible before.

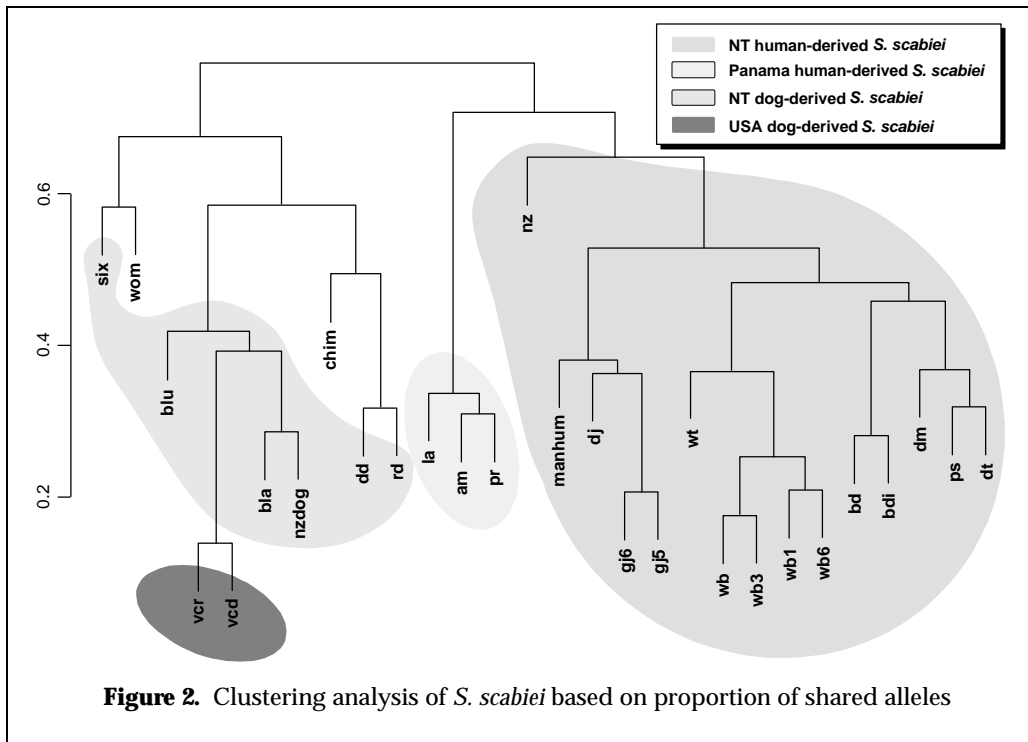
We have been part of the control programs by MSHR in communities in Arnhemland, with community support. Screens were conducted in six communities. We collected skin scrapings from children of all ages judged on clinical criteria to have scabies. We have demonstrated diversity of mite genotypes within a family, within a community and between communities.

Different patients with advanced (crusted) scabies had distinct mite populations. Those re-presenting after treatment with ivermectin [286] were infested with mite populations very similar to those seen initially.

We have examined this question at household and community levels. We have found that the majority (60%) of mites from dogs in scabies-endemic areas are homozygous nulls for the Sarms 20 marker whereas virtually all mites from people bear one or two alleles of Sarms 20.

A set of dog mites obtained from Dr L Arlian, USA, were 100% negative for this marker. In the one household from which we have so far been able to collect mites from both a dog and a baby, the populations were non-overlapping with respect to both Sarms 20 and Sarms 15.

Dendrograms relating all of the mites analysed to date (over 700) revealed that human and dog mites clustered on separate limbs with very little overlap (**Figure 2**).



While these results point strongly to the conclusion that dog and human mites are different we cannot yet exclude overlap and are collecting more data. Nevertheless we conclude at this point that dog mites quite clearly are not contributing to any major extent to the human disease burden. Hence it is unlikely that funds for control of scabies would be well spent on the control of dog scabies.

Community Feedback

Many of the mites were obtained from patients presenting at the Royal Darwin Hospital for treatment for crusted scabies and Dr Bart Currie was involved in counselling. Field studies were largely at Maningrida and the 12 mile camp (Darwin) with Annie Bonson and Peter Thomsen providing Aboriginal liaison. We have only now reached the conclusion that there is a clear difference between the populations. Ms Bev Hayhurst will be involved, together with members of our Aboriginal Unit, in planning and implementing feedback to the communities.

Future Directions

Bev Hayhurst will continue the work of collecting mites from children and dogs from the same households and communities. Pearly Harumal is currently constructing an expression library of cDNA clones from mites obtained from crusted scabies patients. Pearly and Shelley hope to use this set of clones to begin to understand at the molecular level aspects of the immunology of scabies, in particular with respect to the differences in response of normal scabies and crusted scabies patients. The nature of the allergic response and differences between these two groups will be another aspect examined. NHMRC funding for this work until 31 December 2000 has been secured.

Funding

This work was supported by the NHMRC and the Channel 7 Children's Research Foundation of South Australia.

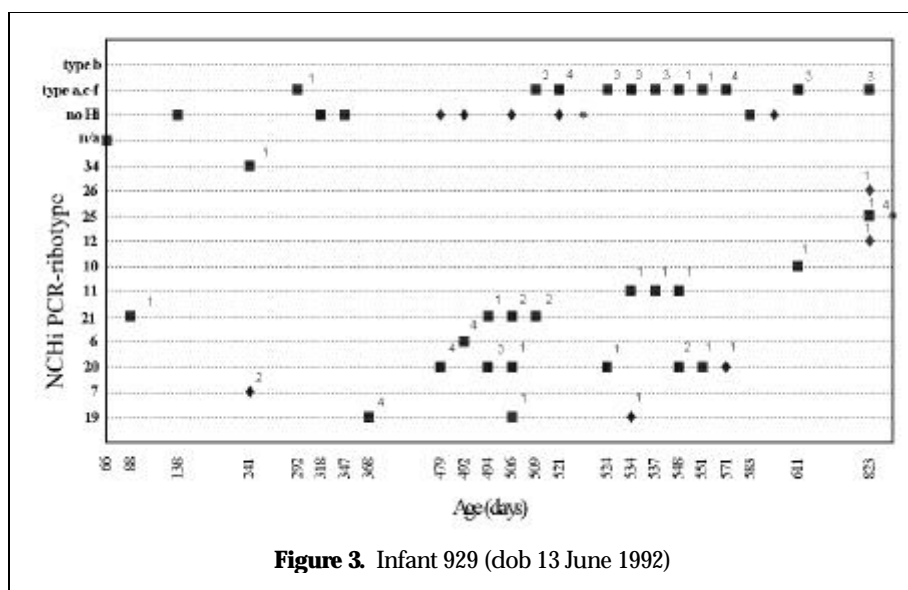
HAEMOPHILUS INFLUENZAE

Molecular Epidemiology of *Haemophilus influenzae*

Aboriginal infants in the Top End of the Northern Territory suffer continuous episodes of otitis media (OM) from within weeks of birth and throughout childhood. A longitudinal study of respiratory bacterial carriage in Aboriginal infants with otitis media in a Top End community demonstrated that the infants become colonised with non-encapsulated *Haemophilus influenzae* (NCHi), *Streptococcus pneumoniae* and *Moraxella catarrhalis* soon after birth and is predictive of otitis media.

Heidi Smith-Vaughan developed a PCR-ribotyping system that she has used to generate a new perspective on the epidemiology of *H. influenzae*. Further analysis of the data is currently being carried out by John Mathews and James McBroom. It was first demonstrated that the extended carriage of NCHi is at least partly due to colonisation with a successive onslaught of different strains, coupled with queuing of multiple strains in each infant (**Figure 3**) [259]. NCHi strains were further characterised by sequencing regions of the P2 major outer membrane protein implicated in protective immunity. Extensive diversity was observed between strains with the extended carriage of a particular PCR-ribotype potentially explained by P2 variation. In addition, horizontal transmission of the P2 gene between different strains was evident [314].

We have now completed the characterisation, by PCR-ribotyping [197] of nasopharyngeal and middle ear discharge NCHi isolates collected from infants and their mothers and siblings. Analysis of these results will allow us to describe the dynamics of NCHi colonisation in this community and the transmission between family members. It will also be possible to determine whether there is an age-specific hierarchy of NCHi colonisation/infection. In addition, analysis of the middle ear discharge data will demonstrate whether certain strains are more likely to invade the middle ear than others.



Hib in the Northern Territory

H. influenzae type b (Hib) isolates were also characterised by PCR-ribotyping, ERIC (enterobacterial repetitive intergenic consensus sequence) typing and by sequencing

loops 4 to 6 of the P2 gene (P2-typing) [387]. The Hib isolates were all identical by PCR-ribotyping and P2-typing to the commonest worldwide strain and the strains that continue to persist in the community at present. ERIC typing split the Hib isolates into 2 groups; ERIC-type A isolates were amoxicillin resistant (β -lactamase positive), with few exceptions, and ERIC-type B isolates were amoxicillin sensitive (β -lactamase negative), which suggests that β -lactamase production in these isolates is chromosomally controlled. Prevalence of amoxicillin resistant strains through 1992 to 1994 did not change although amoxicillin was commonly used. In addition, we detected nonencapsulated *H. influenzae* isolates from before and after the introduction of Hib vaccination that appear to be derived from Hib.

Lipopolysaccharide (LPS) is a major virulence determinant of *H. influenzae*. NCHi are able to display different LPS structures by the spontaneous loss or gain of multiple epitopes in various combinations. Expression of at least three LPS epitopes is encoded by the *lic1* locus. Loss or gain of a variable number of CAAT repeats located within this gene, called phase variation alters the expression of the epitopes it encodes. Louise Martin has detected phase variation of the *lic1* locus in longitudinal isolates collected from an infant colonised long-term with a single strain of NCHi; currently she is examining whether this occurred *in vivo* or *in vitro*. We are continuing to characterise LPS variation in cases of persistent NCHi colonisation/infection.

Community Feedback

Immunisation status including Hib has been closely monitored. Mothers are reminded to take their infants for all immunisations and attention is drawn to overdue vaccines in each child's clinic notes as required. Where colonisation with Hib is detected, or particularly if Hib is cultured from the middle ear, additional attention is drawn to the need for vaccination. At presentations to the clinic staff including doctors, nurses and Aboriginal Health Workers, emphasis on maintaining Hib vaccination is made and carriage status reported.

Future Directions

In order to determine whether elimination of NCHi isolates is related to the development of secretory or systemic antibodies to variable epitopes of P2, P2 fragments of different sequence types have been expressed in pGEX vectors. The next step is to develop sensitive ELISA techniques and examine saliva and sera from the infants and breast milk. So far we have assumed that the differences in colony type are important immunologically without directly demonstrating this.

The P2 sequence information has been used to develop PCR and colony hybridisation assays that will detect low numbers of defined strains amongst large numbers of other bacteria to more precisely define the number of strains carried simultaneously, and the duration of carriage of subsidiary strains queued behind a dominant strain.

Several invasive Hib and NCHi isolates cultured from the blood and CSF of patients at Royal Darwin Hospital have the same PCR-ribotype as strains circulating in the study community. DNA from these isolates will be compared at several different loci in order to determine whether there is some difference between the colonising and invasive strains.

We wish to examine the role of *H. influenzae* serotypes a and c to f strains in otitis media. These strains will be specifically serotyped and PCR-ribotyped, and we will determine the distribution of particular types in nasopharyngeal and ear discharge swabs. We also wish to characterise colonising and invasive strains of NCHi with regard to the adhesins they express.

Funding

This work was supported by the NHMRC.

DONOVANOSIS

A Non-Invasive Diagnostic Test by PCR

Donovanosis is an important cause of genital ulceration that occurs in geographical clusters throughout the world, in particular southern Africa, India, the Caribbean, South America, Papua New Guinea and northern Australia. Diagnosis is problematic as the causative organism, *Calymmatobacterium granulomatis*, cannot be cultured on conventional microbiological media and, until recently, has relied almost exclusively on the detection of typical histological features in tissue smears and biopsies, the sensitivity of which varies between 60-80%. More recently, successful culture has been reported using fresh human monocytes and in our laboratory using a human epithelial cell line [281]. While important for research purposes, culture is expensive, time consuming and is dependent on the careful transportation of the specimen from patient to laboratory. We report here the development by Jenny Carter of a PCR for the detection of *C. granulomatis*, the first major advance in the diagnosis of this disease since 1905. This work was carried out in collaboration with Dr Frank Bowden of THS and with Sri Sriprakash and Sally Rosen of the MSHR.

C. granulomatis and human *Klebsiella* species are ultrastructurally, morphologically and antigenically indistinguishable. Previous analysis of the phosphate porin gene (*phoE*) sequence from *C. granulomatis* by Ivan Bastian and comparison with *Klebsiella pneumoniae*, *Klebsiella ozaenae* and *Klebsiella rhinoscleromatis* showed that there were two base changes unique to *C. granulomatis*. We have found that these base changes eliminate *HaeIII* restriction sites.

Specimens were obtained from patients with a clinical diagnosis of donovanosis who attended remote area health centres. Fourteen specimens from patients with clinically diagnosed donovanosis (9 histologically confirmed), reference isolates of *K. rhinoscleromatis*, *K. ozaena* and *K. pneumoniae*, and 8 samples from patients with unrelated genital conditions (herpes genitalis, syphilis, gonorrhoea, human papillomavirus infection and a mixed anaerobic infection) were extracted for total DNA.

Eleven DNA extracts from patients with donovanosis were subjected to amplification of a 700bp region of the *Klebsiella phoE* gene, encompassing the two unique base changes of *C. granulomatis*.

Amplified products were digested with *HaeIII* and digested products were analysed by agarose electrophoresis. As expected from the sequence data we were able to distinguish the *C. granulomatis*-derived *phoE* product from that of the *Klebsiellae* by the presence of a 167bp fragment resulting from the eliminated *HaeIII* restriction sites. No products were obtained for the 8 samples from patients with unrelated genital conditions.

Using the same PCR and digest conditions, we then targeted the 167bp differential product of *C. granulomatis*. All 8 samples from patients with unrelated genital conditions were negative with this primer set. Band sizes expected from the sequence data were obtained for all 14 donovanosis samples and were again clearly distinguishable from the *Klebsiellae*.

By using a 5' biotinylated oligonucleotide primer we have modified the PCR-*Hae*III digest into a colour test (**Figure 4**) so that it can articulate with the EIA-based PCR diagnostic system currently in place in the Royal Darwin Hospital (the COBAR system) and we are currently developing it for the CAPTAGENE system developed by AMRAD.

Future Directions

This PCR requires further validation in a larger sample of patients using isolates from other countries and then should be implemented at a test site. It should have an important place in the rapidly developing array of diagnostics available for genitoulcerative disease. We hope that the combination of this non-invasive diagnostic test with the azithromycin treatment implemented by Frank Bowden of THS can be used to eradicate this disease from Australia.

Funding

This work was supported by Territory Health Services. Funding has been sought from the NHMRC.



Figure 4. A colour test for Donovanosis. DNA prepared from a clinical Donovanosis specimen was amplified by PCR using a 5' biotinylated primer. The product was denatured, bound to magnetic beads bearing a 20-base oligonucleotide from within the same region and the biotin detected with avidin-peroxidase as for standard EIA tests. The three positives (dark colour) are very easily distinguishable from the 3 negatives.

OTHER WORK

A number of collaborative studies on *Streptococcus pyogenes* [97, 98, 164, 199] (reported on by the Molecular Genetics Unit) and on *Burkholderia pseudomallei* [165, 166, 174] (reported on by the Clinical Unit) have been undertaken.

SIGNIFICANT COLLABORATIONS

Alan Cowman of the Walter and Eliza Hall Institute has collaborated by helping us to establish his *P. falciparum* transfection technology in our laboratory. Prof Larry Arlian of the Department of Biological Sciences, Microbiology and Immunology, Wright State University, Dayton, Ohio, USA and Prof David Taplin, University of Miami School of Medicine, Miami, Florida, USA, both contributed scabies mites for genetic analysis.

Public Health and Epidemiology Unit

John D Mathews, Dorothy Mackerras

The Unit has promoted a broadly based view of public health - with historical, social, cultural and biological perspectives, leading to a broader understanding of infectious and non-infectious diseases and of health care issues. Work with other Units has helped to explain high rates of otitis media and respiratory disease, renal disease, and cardiovascular disease in Aboriginal people as a response to poor nutrition and bacterial infection. It is suggested that vulnerability is greatest in pregnancy, with malnutrition and infection leading to impaired foetal development and low birth weight, which in turn contribute to continuing vulnerability of the infant and child and to chronic disease in later life.

Dr Amanda Lee and Dr Dorothy Mackerras have achieved national recognition for work relevant to Aboriginal nutrition; Dr Mackerras has consulted widely in Australia and overseas on osteoporosis and on food and nutrition policy and practice. In collaboration with Dr Joan Cunningham, now at Australian Bureau of Statistics, she has analysed body size of participants in the National Aboriginal and Torres Strait Islander Survey.

Dr Tarun Weeramanthri, now with Territory Health Services, worked with Ada Parry and other Aboriginal people to develop new ways of presenting mortality information in a culturally appropriate form. He also worked with the coroner and health staff to develop more sensitive procedures for providing information to Aboriginal next-of-kin about coronial processes, autopsies and causes of death.

Ms Mary Dorling has completed an important PhD project on social and cultural aspects of the life of female sex workers in Kupang, Timor. Her results have major implications for the spread of HIV and other STDs in the region.

The Unit has also established theoretical models for infectious and disease processes which provide more understanding than the descriptive models of epidemiology. For example from the longitudinal study, OM in Aboriginal infants developed at an average rate of 16% per day after bacterial colonisation of the nasopharynx, compared with only 2% per day prior to colonisation. Another model suggested that proteinuria (renal disease) developed much more quickly in those with serological

evidence of past streptococcal infection. New models are addressing the epidemiology and population biology of infection with those bacterial species (eg. pneumococcus, group A strep, haemophilus), characterised by multiple serotypes or strains, and still endemic in disadvantaged populations. This theoretical work has profound implications for vaccine development, for the optimisation of antibiotic treatment, and for strategies to minimise the spread of antibiotic resistant strains.

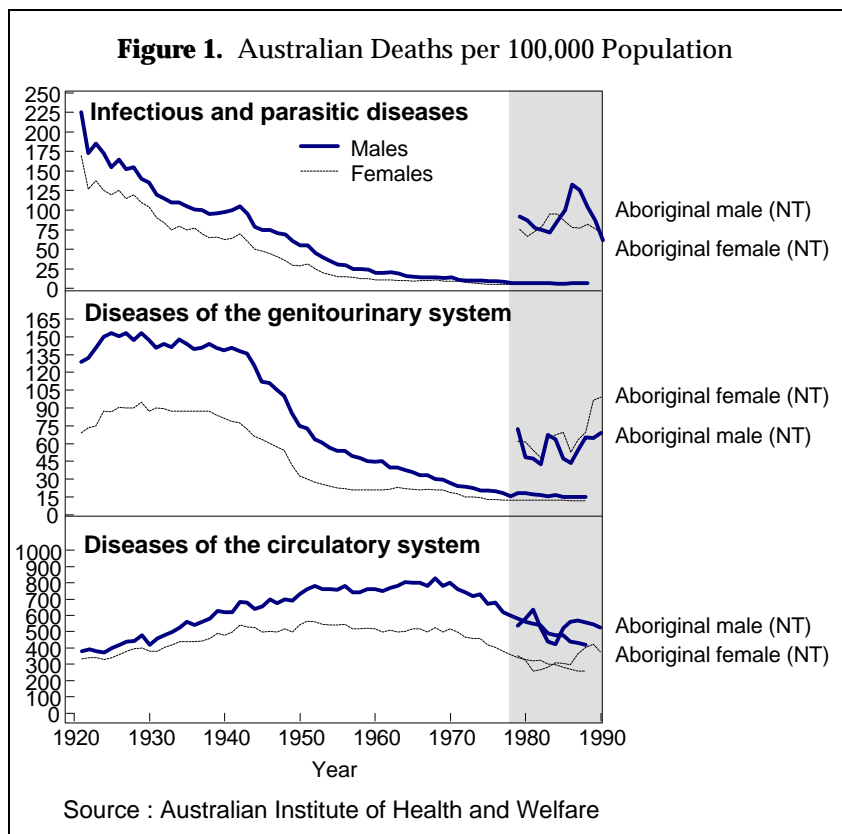
Through Dr Antonia Bagshawe, and more recently through Dr Ross Bailie, the Unit has also facilitated the development of public health coursework teaching. Through John Mathews, Dorothy Mackerras, Tarun Weeramanthri and others, there has been service on national and Territory committees or working groups for NHMRC, the National Heart Foundation, Australian Bureau of Statistics, AIHW, The National Food Authority and the Public Health Association.

SOCIAL AND BIOLOGICAL ORIGINS OF POOR ABORIGINAL HEALTH

[184,185,305]

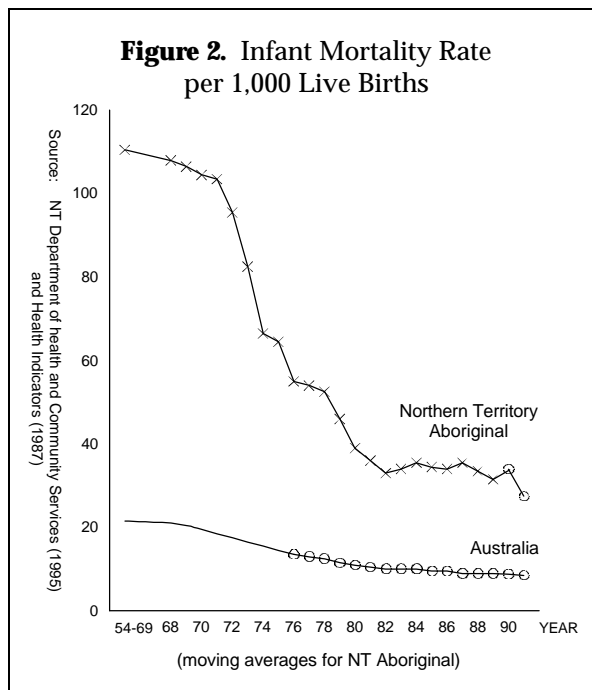
John Mathews, Sue Sayers, Jenny Powers, Joan Cunningham, Wendy Hoy

Time trends in overall Australian mortality rates (**Figure 1**) are comparable to those in other developed countries, with a sharp decline in mortality from infectious diseases, from the 1920s and a later decline in mortality from renal disease from the 1940s and from cardio-vascular diseases in the 1960s.



Recent Aboriginal mortality patterns in the Northern Territory are comparable, in many respects, to those for (non-Aboriginal) Australia in the 1920s, with persistently high rates for infectious disease and its complications, and for renal disease, and high and rising rates for cardiovascular disease (see **Figure 1**), for accidents and sequelae of alcohol use and cigarette smoking [149A, 172, 305]. For infant mortality (**Figure 2**) Aboriginal rates are

still three times greater than those for non-Aboriginal Australians, despite substantial improvements since Aboriginal records were first available in the NT.



Thus the substantial declines in mortality rates and health improvements for Australia as a whole since the 1920s have not been fully shared by Aboriginal Australians. This is because Aboriginal people are socially, educationally and economically disadvantaged, and because their living conditions and facilities for healthy living are still as bad, in many ways, as those in the slums of Australian cities in the 1920s or in third world cities to this day [305].

How do such factors lead to poor health?

Maternal and Infant Health

Social disadvantage is associated with poor maternal nutrition, low birth weight, poor infant nutrition, alcohol use,

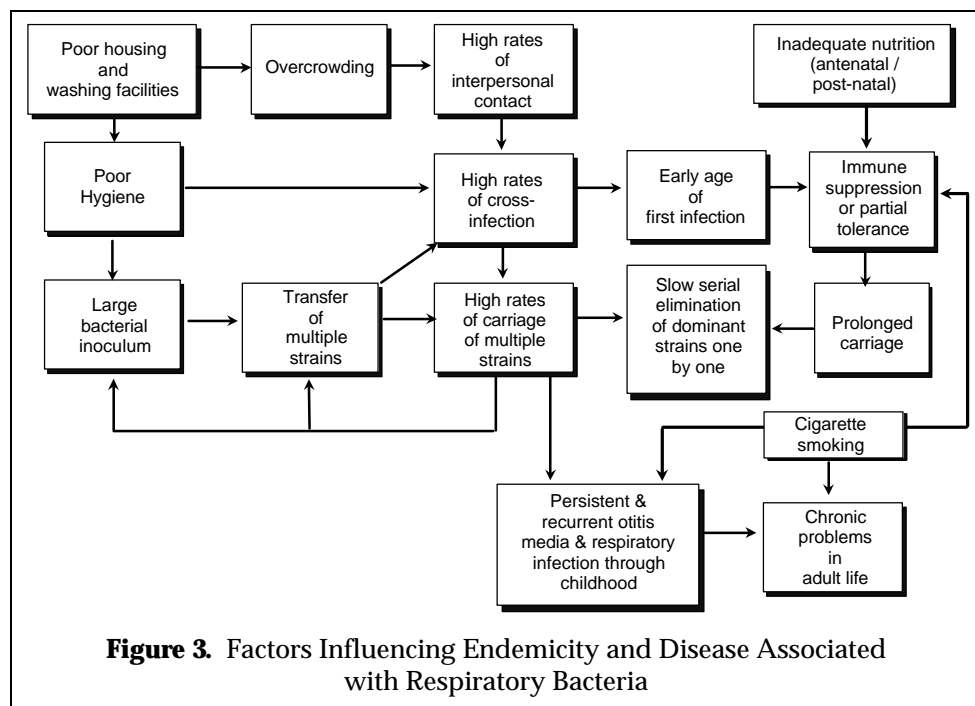
cigarette smoking and with other factors that can adversely affect the infant before and after birth. Aboriginal infants are at particular risk of low birth weight, and malnourished infants have long been known to be at greater risk of diarrhoea and other infectious diseases [184].

Recent overseas work from David Barker and colleagues has also suggested that low birth weight and other measures of intrauterine growth retardation are also predictive of high rates of non-insulin dependent diabetes mellitus, hypertension and heart disease in later life. This association hints at a profound significance of antenatal influences on the risk of disease in later life. An important possibility is that part of the improvement in Australian mortality since the 1920s (**Figure 1**) is due to the effects of improved maternal nutrition on health of the next generation [184, 305]. Reductions in maternal infection in pregnancy may also be important in reducing the risk of low birth weight and of associated chronic disease in later life [305, see below]. Studies by Wendy Hoy, Megan Rees and Emma Kile (see Renal Unit report) already show that low birth weight in Aboriginal infants is predictive of proteinuria, diabetes and increased cardiovascular risk in adult life [184, 359].

Bacterial Infection

Endemic bacterial infections were rife in overcrowded cities prior to the slum clearance programs which ended in most parts of Australia in the years after World War II. Such public programs, together with the introduction of penicillin and other antibiotics, are believed to have played a major part in the decline of respiratory infections and its complications (otitis media, bronchitis, pneumonia, bronchiectasis), skin infections (impetigo), rheumatic fever and rheumatic heart disease, kidney disease and other problems. Aboriginal Australians, particularly in the NT, are still subject to endemic bacterial infection and to high rates for all the chronic complications which have been all but eliminated from non-Aboriginal Australia by a combination of social and medical programs [184, 185, 305]. From the work of Dr Sue Sayers [386A] and others, it seems

likely that bacterial infections are most dangerous in pregnancy, by contributing to intra-uterine growth retardation, foetal impairments and low birth weight, and thus to continuing disease in childhood and later life [184, 305].



Modelling studies (see below and **Figure 3**) have been developed to provide a better understanding of the social, environmental, medical and biological factors underlying bacterial endemicity and chronic disease in Aboriginal and third-world populations.

Alcohol and Cigarettes

Heavy alcohol use, by a minority of Aboriginal men, has had a major impact on rates of domestic violence, accidents and homicides since the early 1970s [225,305]. Cigarette smoking is widespread; its impact on Aboriginal cardiovascular mortality is marked [225], and effects on cancer mortality are now evident [225, 305A].

Health Services

Improved access to antenatal and hospital services for Aboriginal mothers has had a major influence on the decline in infant mortality (**Figure 2**). Improved immunisation and treatment of life-threatening infections has also helped to reduce acute childhood mortality, but primary health care services have not improved sufficiently to impact on morbidity and mortality from the chronic sequelae of malnutrition and infection [225, 305]. Likewise because of the high rates of hypertension, diabetes, renal disease and heart disease, and because of resource limitations and difficulties of service provision across the cultural interface, many Aboriginal adults are not yet receiving adequate care for these important medical conditions [305]. Similarly, cancer mortality rates for Aboriginal people are rising, and the ratio of cancer mortality to cancer incidence is high [305A], probably because of poor availability and uptake of services leading to poor diagnosis and poor treatment. The *Health Service Issues* box (p. 90) identifies some of the important

Health Service Issues

Difficulties with the delivery of best practice health services in remote and rural Australia are related to the small and dispersed population, to diseconomies of scale, and to problems with the retention of skilled staff to live and work outside of the major capital cities. Provision of health services for Aboriginal Australians is made even more difficult by :

1. Lack of understanding by politicians and decision-makers of :
 - the factors contributing to poor Aboriginal health;
 - the prerequisites for change -
 - Aboriginal control to ensure that services are culturally appropriate;
 - adequate funds and resources for -
 - education and training of Aboriginal people;
 - recruitment and retention of non-Aboriginal health professionals;
 - sufficient time (days to generations) for the improvement in health service to be translated into an improvement in health outcomes.
2. Lack of understanding by many Aboriginal people of :
 - the magnitude of their health disadvantage and their high level of need for health services;
 - the potential value of lifestyle change, preventive health programs and clinical services in improving health;
 - the particular changes in lifestyle that would help to improve their health;
 - the support that should be available to bring about lifestyle change;
 - the particular preventive measures and clinical services that should be available.
3. The poor supply of health services for Aboriginal people relative to their level of health need (resulting from 1).
4. The cultural inappropriateness of many health services (resulting from 1).
5. The limited demand for health services by Aboriginal people, relative to their high levels of health need, has been used as an implicit rationale to limit the supply of services.
6. The limited uptake of services that are available because they are culturally inappropriate or inaccessible.
7. The limited compliance with, or adherence to, the lifestyle changes and treatments that are recommended by health services.
 - **Aboriginal people have a greater health need because they are less healthy than other Australians.**
 - **Despite this, there are less services available for them.**
 - **Aboriginal people consume less services, relative to their health need, than other Australians.**

factors that impede the delivery of more effective health services for Aboriginal people. Particular health service projects are described in separate reports from the Central Australian Unit, the Clinical Unit, and the Health and Social Science Unit of the School.

How Long For Aboriginal Health to Improve?

There can be a latent period of a generation between some causal inputs (eg. maternal malnutrition and infection in pregnancy) and some health outputs (eg. kidney disease or heart disease in the next generation). Accordingly, such health problems may take a generation to improve, even if health services and preventive programs improve overnight! It is thus unreasonable to require that preventive health services be shown to be effective in improving health outcomes in the short term. They should be provided and funded because that is the right thing to do!

ABORIGINAL MORTALITY : A CULTURAL AND EPIDEMIOLOGICAL APPROACH

Dr Tarun Weeramanthri, in collaboration with Norma Benger, Ada Parry, Clifford Plummer and Vicki Nangala-Tippett, and with support from PHRDC and THS, and cooperation from many other people, coordinated a detailed examination of issues relating to deaths of Aboriginal people. [64-67, 69, 131, 133, 134, 204-206, 252, 267-269, 325,326 and *High Rates of Aboriginal Mortality* box].

Community Responses to Unexpected Deaths

The mortality team found that in Aboriginal communities, deaths which were otherwise unexpected could be an important trigger for community discussion and social action. For example sudden deaths from heart disease triggered the community concern at Minjilang which led to the successful community nutrition program organised by Daisy Yarmirr, Annie Bailey and Mandy Lee [103]. Amongst examples in other communities were responses to hypertensive stroke, with a call for blood pressure screening, and to advanced cervical cancer, followed by a call for cervical screening. These examples suggest that the emotional and social effect of unexpected deaths can be channelled by communities into their own programs aiming to promote social change and health development.

The **mortality team approach** has been to discuss these issues with Aboriginal people, and to work to provide culturally appropriate knowledge about individual deaths and about mortality patterns, so that communities are as fully informed as possible. The meaning to be attributed to this knowledge is thus derived from traditional cultural beliefs as well as from the paradigm of scientific medicine [133]. **Knowledge about individual deaths** has often been difficult for next-of-kin to obtain, because of poor communication, and because of long delays in the coronial process with the intrusion of police and forensic pathologists into a relationship that would otherwise only involve the family with Aboriginal health workers or other health professionals serving their community. The team has already been able to make recommendations to the police, coroner and health services to improve the quality and timeliness of feed-back to next of kin [65, 67, 131, 133].

High Rates of Aboriginal Mortality

The essential facts are now fairly well-known.

Life expectancy for Aboriginal people is reduced by 15-20 years.

Death rates are rising in the 25-50 year old age group which shows the greatest rates relative to those of non-Aboriginal people of the same age.

Infant death rates have fallen with improvements in medical services, but are still three times greater than those for non-Aboriginal Australians.

Major medical causes of death are heart disease, injuries and accidents, and lung problems reflecting poor nutrition, smoking, social disruption, alcohol and infectious (bacterial) disease.

A Language to Improve Communication

To help with cross cultural communication, the team has extended the conceptual framework of Body, Land, Spirit to link Aboriginal concepts to the disease-based framework of western medicine [133, 204, 205, 206 and *Body, Land and Spirit* box].

Public Health Audit of Adult Aboriginal Deaths

The emphasis in reporting was to use simple statistics relating to numbers and causes of deaths (including alcohol-related deaths [134]) in the different districts within each region. Proportion Mortality Ratio (PMR)_{<50} is the proportion of all people dying, aged under 50 at death. The PMR_{<50} for Australia is about 12%. The PMR_{<50} for NT Aboriginal people varies between 39% and 55% in the three regions. PMR_{<50} is generally higher for males than females and in urban districts.

Alcohol-related deaths are prominent, especially in men under 50 years at death and explain some of the variability in mortality between communities [134]. Diagnostic errors are infrequent but around 15% of death certificates are filled out poorly in all regions, leading to potential problems with cause of death statistics. Ada Parry and Norma Benger distributed the mortality information widely at community level in a culturally appropriate manner [205, 206, 267, 268].

Study of Forensic Autopsy Data

A retrospective review of coronial records of 179 Top End adults who came to coronial autopsy showed that the rate of sudden death coming to autopsy was 7.5 times higher for Aboriginal people than for non-Aboriginal people. Coronary atherosclerosis was the cause of 37% of the Aboriginal sudden deaths and 52% of the non-Aboriginal sudden deaths [269].



Body, Land and Spirit*		
Aboriginal Concept	Western Concepts	Causes
BODY	eg. Diabetes Hypertension Heart disease	Poor quality western food Too little exercise
LAND	eg. Chest infections Rheumatic fever Diarrhoea Chronic diseases . ears/chest . heart	Poor housing, water and sanitation Overcrowding Poor hygiene Inadequate health care
SPIRIT	eg. Social anomie, Alcohol problems, Accidents, domestic Violence, suicide, Homicide	Cultural dislocation Unemployment Poverty Poor education
SMOKING	Lung cancer Heart disease Chronic bronchitis	
*With acknowledgments to Prof Jan Reid, Dr David Scrimgeour and Dr Ben Bartlett.		

Mortality amongst Diabetic Aboriginal People

Dr Christine Phillips and Dr Mahomed Patel (Territory Health Services) worked with Tarun Weeramanthri to identify the causes of death for known Aboriginal diabetics in Central Australia. Diabetes was associated with an increased risk of mortality (2.09 for men and 1.69 for women) compared with overall Aboriginal rates for the Northern Territory. Renal disease was the direct cause of death in 22% of cases, infection in 21%, and ischaemic heart disease in 14%. Death certificates were inadequate : 44% made no mention of diabetes. Furthermore, the contribution of renal disease was underestimated by Australian Bureau of Statistics coding which recorded it for only 20% of the certificates on which it was mentioned. Diabetes appeared to amplify the effects of infection and renal disease amongst Aboriginal people [191].

Accuracy of Death Certification

In parallel studies, Dr Weeramanthri showed that although there was no shortage of diagnostic information, there are shortcomings in at least 16% of death certificates because of inexperience in certifying doctors. Specifically, with the need to specify only a single cause, doctors often choose the wrong one. A major error was to omit any mention of alcohol when it was clearly involved in the death. The utility of the death certification could be improved by providing more information for doctors and by making provision for multiple cause coding [325, 326].

Emergent Issues

A number of issues emerged that have become the basis for ongoing discussion and research with Aboriginal communities and other agencies. These include the high rates of alcohol-related deaths, the high rates of mental illness, particularly amongst men, the

need for community action on cigarette smoking, and the need for more intersectoral cooperation in providing resources and services so that social action can be planned and managed at community level by Aboriginal people themselves.

Dr Weeramanthri completed his PhD thesis entitled “*Out of Sadness, Hope*” as a descriptive and critical study of the production and use of mortality statistics relating to adult Aboriginal people of the Northern Territory. It was based on the belief that a death can be an opportunity for professional and community reflection on the best ways to prevent a similar death in the future. It utilised an intensive case-study approach to describe and interpret the deaths of 220 adult Aboriginal people who resided and died in the NT in 1992 [326].

There were two main parts to the thesis: a medical cause-of-death validation study and a description of how a medical audit can be transformed into a audit with broad public health implications. The thesis attempts to ‘make death meaningful’ through consideration of the links between Western and Aboriginal experiences, concerns, systems and worldviews. It was argued that improved understanding of the similarities and differences between these worldviews will enhance communication and respect between health professionals in the NT and the community they serve.

Dr Weeramanthri is now the Manager of the Chronic Disease Network in Territory Health Services, with an ongoing involvement in public health teaching through Menzies, and in CRC research.

Mortality Patterns and Potential Years of Life Lost

Following on from THS work on causes of mortality and hospitalisation in the NT, Joan Cunningham examined the trends over the years from 1979 to 1991, and compared the rates and years of potential life lost in the Aboriginal and non-Aboriginal people [149, 225].

ABORIGINAL GROWTH AND NUTRITION

Minjilang and Related Projects

Amanda Lee completed several important nutritional projects in partnership with Aboriginal communities. The PHRDC-funded work leading to her PhD. has received wide recognition. In response to a request from Daisy Yarmirr and others from Minjilang to help the community to improve its nutritional health, she developed a method for using information about the sale of food in the community store as a surrogate for intake at the community level [104, 181]. This was validated by showing that when the quantity of nutrients in the food supply changed, so too did the blood levels in the people living in the community [38, 103]. There are certain limitations to the ‘store-turnover’ method, for example it cannot be used if information about the nutritional intake of an individual is desired, but it has been widely adopted by other Aboriginal groups for doing community-level assessments.

Following on from this, she evaluated the nutrition policy for Aboriginal community stores developed by the Arnhem Land Progress Association and examined the effect of different store managers on the food sold [241, 242]. She found that the amount of fruit and vegetables sold depended on what was available and that a popular preconceived notion that Aborigines would not buy these foods was quite wrong.

The sudden deaths from heart attack of several young men had been the stimulus to the Minjilang community to ask for health promotion strategies to prevent further deaths. Investigation found that cholesterol levels were high and blood levels of micro-nutrients such as beta-carotene and folic acid were low. Working with Aboriginal people, an intervention program was devised. One major aspect was a change to many of the types of food sold through the store, increases in the amount of fruit and vegetables offered for sale, introduction of good food workers into the store and various ways of promoting the preferable choices. Short-term evaluation showed that cholesterol levels declined and micro-nutrient levels in the blood rose [103]. There were also improvements in other subjective and objective measures of health, the community was pleased with the results [103], and many of the improved outcomes were sustained in the longer term without external support; three years after the intervention, many of the changes in the store had been retained [180].

Aspects of this project have now been incorporated into some Territory Health Services nutrition programs. For example, information about how stores function from the management viewpoint has been developed as part of a strategy to encourage communities to adopt policies about the types or quantities of food sold in the store. A video has been made by THS covering various aspects of healthy store food and consumer rights.

GROWTH AND BODY SIZE IN INDIGENOUS AUSTRALIANS

The relationship between obesity in adults and the increased risk of diseases such as heart disease and diabetes is well known. As these diseases are now major causes of mortality in Indigenous Australians there is a particular focus on preventing further increases in overweight. However, underweight in infancy and childhood may also increase the risk of these diseases. Many overseas studies have found that diabetes and heart disease are more common in those who were underweight in relation to length at birth. In a study with Tiwi people, Dr Wendy Hoy and colleagues have shown that low birth weight and poor growth in the first year of life increase the risk of renal disease in early adult life, even after allowing for the effect of adult obesity [265A and see Renal Unit report].

Underweight in young children is well known to increase morbidity and hospitalisation rates. It can also lead to short adult stature which is well known to increase the likelihood of having a low birth weight infant. Thus underweight not only affects a child's short-term health, it may also affect its long-term health and the health of the next generation [184, 265A, 305].

Body Size in the NATSI Survey

Underweight in Aboriginal infants in remote Australia has been documented for at least 30 years. Less is known about those in urban areas, although weights at birth and through infancy seem better for Aboriginal infants in Darwin than for those in rural communities [309]. The height and weight data from the 1994 National Aboriginal and Torres Strait Islander Survey, the first nationally representative survey of Indigenous Australians were analysed to examine differences by ethnicity and location of residence [343].

Describing the size of adults is relatively easy, as there are widely accepted definitions for categories of body mass index (BMI) for this group. Torres Strait Islanders have a higher prevalence of overweight and obesity, according to these criteria, than Aborigines (**Table 1**). However, there is some debate at present over whether the same BMI cutpoints should be applied to all racial groups. For example, earlier work has indicated that Aboriginal women with a BMI of 24 have the same proportion of body fat as a Caucasian with a BMI of 25. Others have found that a BMI of around 30 in Polynesians is equivalent, in body fat terms, to a BMI of about 25 in Caucasians. These were small studies, and Torres Strait Islanders are Melanesian, not Polynesian; but they do raise the possibility that Aborigines have a higher prevalence of true obesity even though the prevalence of BMI greater than 30 is higher in the Torres Strait Islanders. This is clearly something that should be looked into further so that appropriate advice can be given to the Torres Strait Islanders.

Describing the size of children and adolescents is much harder as there is no single reference curve for the ages 5-17 years. We had to use 4 different references. Compared to the international reference growth curve, children aged less than 11 years were short for their age, especially in the rural areas (**Table 2**). Mean weight was low for age outside the capital cities, however mean weight was not low in relation to height, and in capital cities was quite high. This indicates that the major growth problem is due to stunting, which indicates a chronic low level problem. That this occurs in capital cities, and not just in remote areas, is noteworthy.

Body mass index was used to describe size in children aged 7-15 years. The proportion falling below the 5th centile or above the 95th centile from a nationally representative survey conducted across Australia in 1985 was calculated. If the two populations were the same, then 5% would be expected in these groups. However, in NATSIS, 15% of boys and 11% of girls were below the 5th centile and 13% of boys and 19% of girls were above the 95th centile. Underweight was much more common in rural areas, and overweight was a little more common in capital cities. This indicates that there is an excess of both underweight and overweight in this age group.

Underweight in children is not widely discussed in Australia although there is great discussion about the increasing prevalence of overweight. These results show that if surveillance of body sizes in children focuses only on high values (*ie.* overweight), it will miss detecting the existence of an important public health problem and may lead to inappropriate programs being delivered to some groups.



Table 1. % of the adult population with obesity (BMI ≥ 30 kg/m²) by age, sex and ethnicity, NATSIS, 1994 (from Cunningham and Mackerras, 1998)

Age	Aboriginal	Torres Strait Islander	All Indigenous
Men			
18-24	17	35	18
25-44	26	49	27
45-64	28	41	29
65 or older	13	23	14
Total	24	43	25
Women			
18-24	21	45	22
25-44	26	54	28
45-64	39	48	39
65 or older	26	55	29
Total	27	50	29

Table 2. Mean z-score and standard deviation (SD) of children aged 5-9 years measured in the NATSIS, 1994 (from Cunningham and Mackerras, 1998)

	Height-for-Age		Weight-for-Age		Weight-for-Height	
	mean	SD	mean	SD	mean	SD
Boys						
Capital city	-0.29	1.3	0.35	1.6	0.98	2.8
Other urban	-0.54	1.7	-0.11	1.7	0.48	2.6
Rural	-0.53	1.6	-0.30	1.7	0.16	2.6
Girls						
Capital city	-0.19	1.5	0.42	1.9	0.93	2.4
Other urban	-0.41	1.4	-0.13	1.4	0.29	2.4
Rural	-0.53	1.6	-0.20	1.6	0.20	2.1

Analysis of 10 Years of Growth Data from the Katherine Region

The NATSIS did not measure children under the age of 5 years. Surveys of children under 5 years have been conducted 4 times per year for 10 years in the Katherine district. Approximately 13,000 weights, and slightly fewer heights, had been collected on about 2,500 children. These were converted into z-scores to allow children of different ages to be compared. Plotting the data revealed that growth was excellent in the first 4 months of life and that growth failure started at about 4 months. Children started to grow at a normal rate at about 14 months of age but did not at an accelerated rate to allow deficit generated between 4-14 months to be reversed. Hence they remained short and light for their ages.

A mixed effects regression was done to allow for the multiple measurements on each child to determine whether there had been an improvement in growth over time and whether the impression that there was a seasonal variation was, in fact, correct. This analysis confirmed that weight was lightest in December and March and heaviest in September. Although there had been a slight improvement over the 10 years, it was less than the annual variation between December and September. These effects were small in

relation to extent the growth failure, although sufficiently large that season of the year should be taken into account when collecting data to evaluate an intervention program over a short period of time. One consequence of this is that the effort spent in doing frequent screening could be redirected into other approaches to address the problem.

At present, only the data for children aged 16-60 months has been analysed because the data for younger children may be influenced by birthweight and gestational age at birth which are not available. The dataset is currently being matched to the Midwives Collection to obtain as many of these as possible. This will allow an assessment of whether the decline in rate of growth between 4-12 months occurs in all children or to a greater extent in low birthweight and/or preterm and/or children with intra-uterine growth retardation and hence what recommendations about targeting of follow-up for particular groups of children might be needed.

Community Feedback and Future Directions

At present, studies are in train to find the best ways of presenting statistics about child growth back to communities. This work is connected to the Growth Assessment and Action strategy of Territory Health Services. The data have shown that the action needs to be taken earlier than is often thought. Specific strategies and programs are needed at individual and community level to promote the growth of children in the second half of infancy. It is likely that this will be adopted as a major theme for Child Protection Week in September 1998 as a way of focusing community attention. Recently, THS has revised the chart used for monitoring child growth and Food and Nutrition Policy Unit is currently running workshops explaining the changes to doctors, nurses and Aboriginal Health Workers. One of the main changes to the chart should lead to earlier identification of children who are exhibiting growth failure. There are also plans to collate the data centrally for surveillance with not more than two collection occasions per year. Funding for this study was provided by Territory Health Services.

EVALUATION OF THE PILOT PHASE OF THE STRONG WOMEN, STRONG BABIES, STRONG CULTURE PROGRAM

Dorothy Mackerras received a grant from THS to analyse data collected as part of the well-known Strong Women, Strong Babies, Strong Culture Program [368]. The first workshop for the Strong Women Workers from the 3 pilot communities was conducted in August 1993. **Figure 4** shows that there was a marked change in the mean birthweight of infants born in the 3 pilot communities after the Program started compared to Aboriginal infants born in the remainder of the rural Top End.

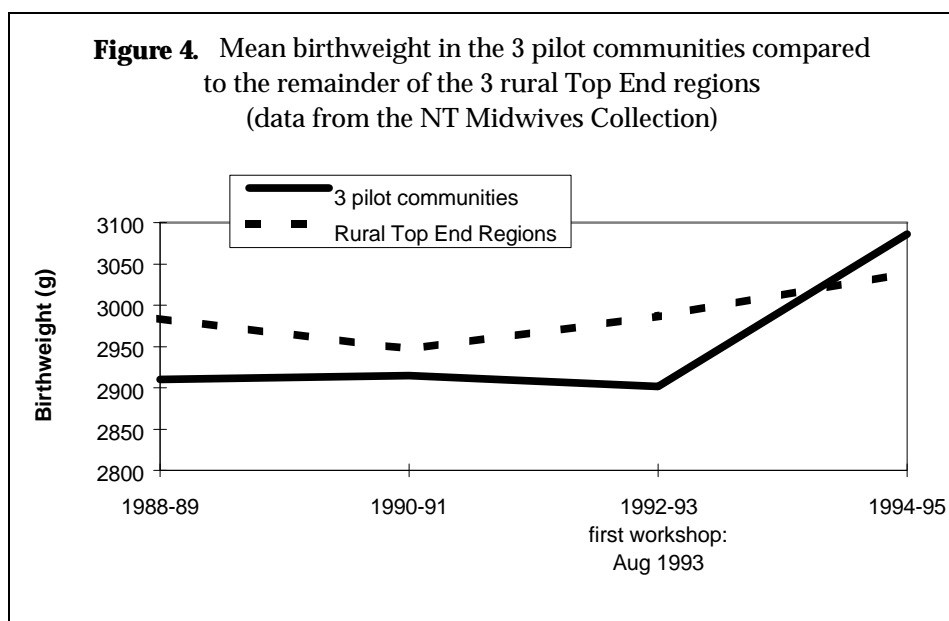
Analyses of data extracted from clinic records in the 3 pilot communities showed that there was an increase in maternal weight of about 2kg which contributed to part of this effect. There was also a marked drop in the pre-term rate, however there was a substantial discrepancy between this and similar data in the Midwives Collection. Interestingly, this evaluation found a substantial increase in the number of genital infections diagnosed in 1996. This coincides with the field-trial of self-administered collection of specimens using a tampon. It was not related to the decline in preterm births but this may have been due to the way genital infections were grouped together during data extraction.

As communities known to have high rates of low birth weight were specifically targeted for the pilot phase, this evaluation does not allow the effect to be directly attributed to the

introduction of the Program rather than a coincidental change. However, the results are positive and certainly enough to support expansion and further evaluation of the Program.

Community Feedback and Future Directions

At this stage, the results have been presented to Strong Women Workers, health staff and the council in two of the three pilot communities. There will be further dissemination through the Program coordinators and to other interested parties. The recent NT budget allocated funds to allow the Strong Women, Strong Babies, Strong Culture Program to be expanded to many more communities. The report made recommendations about future evaluation of the Program, in light of the fact that there was no data collected from comparison communities during the pilot phase. This evaluation was funded by Territory Health Services.



INFECTIOUS DISEASES

Hepatitis B Virus Infection

After earlier studies of hepatitis B in Northern Territory schools carried out by Dr Ian Gardner, further studies of HBV were carried out by Xinan Wan, as a postgraduate research student. He documented the occurrence of acute hepatitis B in young Aboriginal children in whom it is often asymptomatic, the more severe acute disease seen in non-Aboriginal adults [62, 63], and the very high rates of liver cancer (hepatoma), presumably due to early hepatitis B infection, in Aboriginal adults [130]. Mr Yuejen Zhao worked with Xinan Wan, Jenny Powers and John Mathews, to develop statistical models to explain the frequency of hepatitis B described in a published report from the Brewarrina community of NSW. They found that 20-30% of Aboriginal people were presumably infected with hepatitis B virus from the mother, soon after birth, and that viral carriage persisted for many years thereafter. Those who escaped infection at birth were apparently infected at an average rate of 10% per year thereafter, although after such infection the virus persisted for only a few weeks rather than for many years. Rates of infection for non-Aboriginal residents of Brewarrina were very much less than for Aboriginal people.

These studies helped to support the very strong rationale for hepatitis B immunisation to prevent infection, particularly for Aboriginal Australians, for those moving into such communities, and for others at risk. Partly as a result of this research, THS introduced universal HBV infant vaccination in the Northern Territory.

Dr Wan has also worked with colleagues from the NT Dept of Health and Community Services (Dr Steve Guthridge and Dr Jan Bullen) and with Bart Currie and John Mathews to evaluate the response to the hepatitis B immunisation program for Aboriginal infants introduced in 1989. As in other similar studies, Aboriginal infants appeared to respond less well to the standard three doses of the vaccine given, although the response to a fourth dose of vaccine was very good in those who had inadequate responses after the third dose. Despite these uncertainties, the pattern of results suggested that hepatitis virus transmission had been greatly reduced following the introduction of the vaccine program.

HTLV-I Virus

Dr Ivan Bastian completed his PhD thesis on the epidemiological and molecular aspects of HTLV-I infection in Australia and nearby countries [111] and he also evaluated tests for screening and diagnosis of HTLV-I infection within Australia [5, 6, 7]. A fascinating observation was that the wife of an HTLV-I positive blood donor showed an unusual (equivocal) reaction on HTLV-I screening without herself being positive for the virus. This suggested that the wife might have been exposed to the virus from the husband without being infected or that she had been infected and that the virus had been killed by the immune response. This crucial observation, could provide a rationale for a vaccine to prevent HTLV-I infection, which is an important health problem in some Aboriginal populations, in Southern Japan and in parts of the Pacific region [111].

Diagnosis and Treatment of Donovanosis

Dr Ivan Bastian worked with Dr Frank Bowden from Territory Health Services to start a program of research that eventually led to new means for detecting and treating donovanosis, a disease that causes genital mutilation, predominantly in men. In Australia, donovanosis is only reported in Aboriginal patients in the tropics. The work led to a PCR-based sensitive diagnostic method using swabs rather than biopsies and to the successful culture of the organism in a laboratory for the first time in Australia and only the second time in the world since 1962 [214, 281, 341, 342]. The improvements in diagnosis, together with the introduction of more effective treatment with azithromycin by Dr Bowden, should enable the eradication of donovanosis in northern Australia within a very short period of time. The very exciting molecular work is described more fully in the report of the Molecular Parasitology Unit. Funding for this project was provided by CARG.

The T-test and PCR to Diagnose Genital Infections

Prior to November 1995, genital infections in women were usually assessed using a vaginal endocervical swab with microscopy and/or culture. This allowed good detection of infections such as thrush and *Gardnerella vaginalis*, but only about 50-60% of the Chlamydia and about 10% of the gonorrhoea could be picked up this way. Trichomonas infections were usually missed, unless they happened to be present on a Pap smear. A collaborative project between MSHR, the AIDS/STD Unit of THS, Monash University

and the Royal Women Hospital in Melbourne has tested Aboriginal women's menstrual tampons by PCR to diagnose genital infections.

In the first 6 months of 1996, a large field trial involving approximately 600 women in various communities in the Top End. This proved to be valid and acceptable to the women [276A]. Of the women tested, 6% had Chlamydia, 20% had gonorrhoea and 22% had trichomonas. The T-test was being widely used in Aboriginal by late 1996. Another field trial was conducted to investigate whether genital infections could be detected more effectively from a urine sample than from tampons. However, urine sampling was not more effective and it was less acceptable to women.

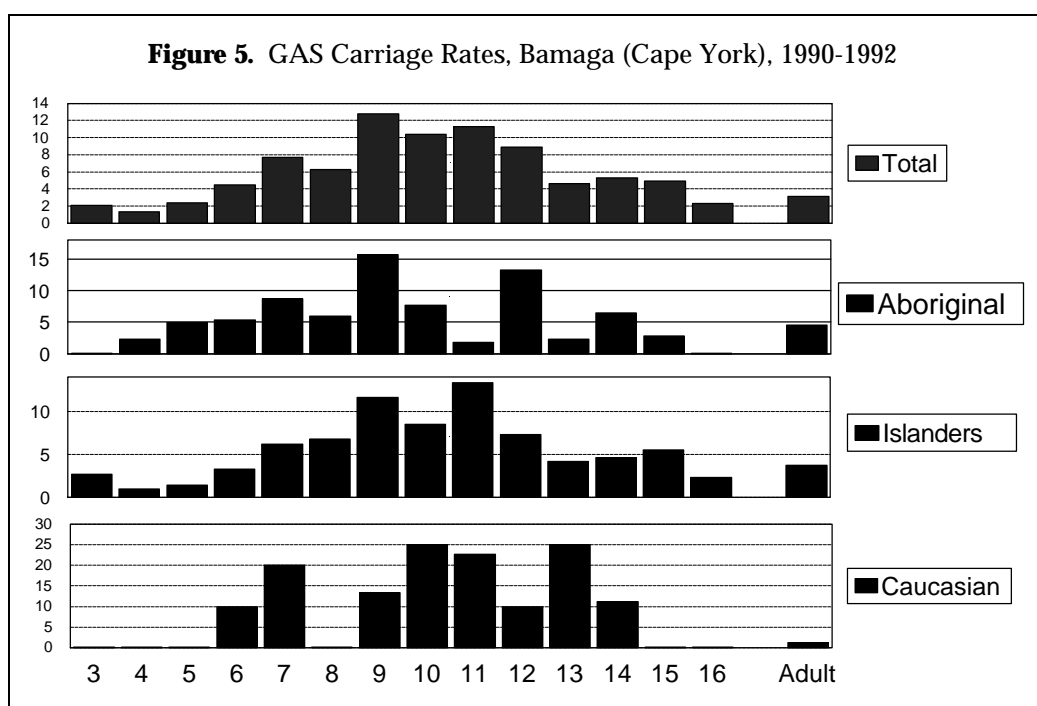
A survey of 1200 women in late 1997 by T-test showed a reduction in Chlamydia prevalence to 4-5%, to 17% (trichomonas) and to 10% (gonorrhoea), compared to the results in early 1996. This suggests that there has been a decline in the prevalence of infections, presumably due to increased detection and treatment, between 1996 and 1997.

New Strategies for Trachoma Control

Andrew Laming, Bart Currie, Amanda Leach, Peter Morris, Andrew Bell (THS), Jonathan Carapetis, Annie Bonson, George Kruger (THS), Hugh Taylor (Uni Melb), John Mathews

Overseas studies from Gambia and elsewhere have shown the value of azithromycin, a long-acting macrolide antibiotic, for the community control of trachoma. Azithromycin has now been accepted as one of the standard treatments for trachoma in the Northern Territory. Andrew Laming, an ophthalmological trainee, has worked with staff of Territory Health Services, and with the Lajamanu community, to evaluate the effectiveness of azithromycin for clinically diagnosed trachoma in Aboriginal children in the Northern Territory.

The most important outcomes from the study have been to provide local information about the apparent rate of "cure" after single-dose azithromycin, and to estimate from follow-up studies, the rate of clinical relapse or reinfection [178]. These data can then be used in modelling studies to estimate what frequency of treatment might be needed to eliminate trachoma or to reduce the prevalence to such an extent that it can be controlled



by offering treatment on a "case by case" basis alone, without the need for special screening.

Ancillary outcomes have come from studies of nasopharyngeal carriage of respiratory bacteria before and after treatment with azithromycin. In the short term carriage rates of *S. pneumoniae* have been dramatically reduced, whereas by two months they have risen again [298, 365], with a rise and fall of azithromycin resistant strains following treatment.

Epidemiology of Group A Streptococcal (GAS) Infection

Don Gardiner, Bill Glavin (Qld Health), Lexine Schafer (Qld Health)

Don Gardiner, in collaboration with Torres Strait colleagues, surveyed the population of Bamaga, North Queensland, for throat carriage of GAS at intervals of 3-4 months in 1990-92. Children found to be carriers were treated with benzathine penicillin. Throat carriage rates of GAS, averaged over the six surveys, are summarised by age and ethnic group in **Figure 5**. For each ethnic group, the carriage rates increase with age until approximately 10-12 years and then decline at older ages. On average, carriage rates are higher for Caucasian children than for Aboriginal and Islander children attending the same school. In contrast, carriage rates for Caucasian adults are lower than for Aboriginal and Islander adults at Bamaga.

These findings are of particular interest because for Aboriginal children in the Northern Territory, GAS carriage is much more frequent on the skin (and associated with impetigo) than GAS carriage in the throat. Such differences will only be fully understood by studying the strain-specific dynamics of GAS infection. Traditional serological typing methods of GAS are of limited value in the context of the Northern Territory due to the large number of non-typable strains, as well as serological cross-reactions which produce misleading results. New molecular typing methods developed at Menzies, RAPD analysis and Vir typing, are being increasingly used to study the way in which specific GAS isolates interact with the population.

Using these two PCR-based molecular typing methods, with confirmatory sequencing of the emm gene in prototype isolates, a clearer understanding of the infective load in Aboriginal communities is emerging. Up to 13 different strains of GAS have been identified at the same time in a single community (see Molecular Genetics Unit report) and it is now possible to gain a better understanding of the natural history of streptococcal disease in these communities. It now seems that a particular GAS strain will persist for some weeks in an infected skin sore if untreated, and that in any rural community, not all children will become infected with every passing GAS strain; each strain tends to persist for some months in each community. Detailed modelling of GAS carriage rates following treatment of trachoma with azithromycin [178, 298, 365] suggests that there is cross-immunity between different GAS strains, and that immunity from endemic skin infection might help to explain the lower rates of throat carriage in Aboriginal communities. Molecular typing methods have also been used to study streptococcal strains associated with an outbreak of APSGN in three Aboriginal communities in mid-1995, in an effort to identify the causative organism.

MODELLING OF INFECTIOUS DISEASE PROCESSES

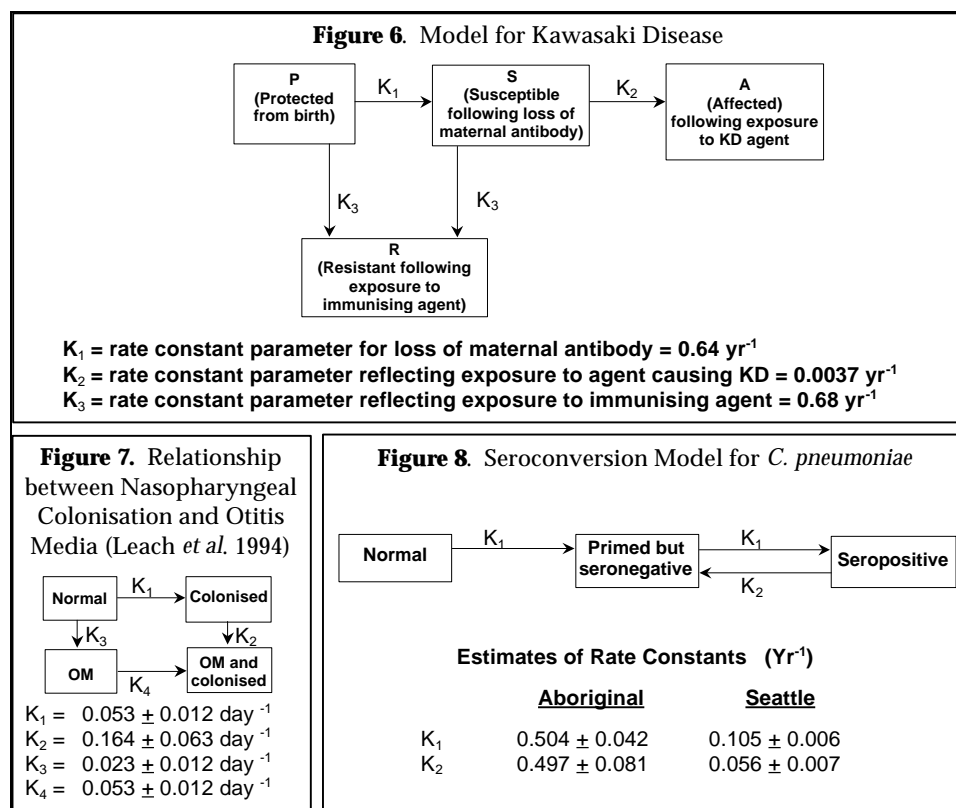
Epidemiological modelling can help to test causal hypotheses about disease processes. In simple terms, an epidemiological model makes biologically plausible assumptions about how particular observations **might** be generated by particular (disease) processes, and

then carries out statistical tests to see which of the assumptions are required in order to explain the observations. Those assumptions which are not required can be dropped from the model. Thus, a modelling exercise can never **prove** a particular (hypothetical) pathway or process, although it can, at least in a limited sense, **disprove or falsify** the assumption that a particular pathway or process is important. More specifically, the importance of a pathway can often be measured by the magnitude (with confidence intervals) of a parameter measuring the rate of that process in time. (eg. **Figure 3**, page 89)

EPIMOD Computer Package

Mark Daly, Mary Pat Reeve, John Mathews

A flexible computer program (EPIMOD) has been developed to allow for automated fitting of epidemiological models for hypothesis-testing. Modelling is conceptualised in terms of multiple states or stages connected by transition pathways (see **Figures 6-8** for simple examples). Transition from one state to the next is assumed to proceed at a rate that may be constant (with a fixed parameter K_1 , say, to be estimated), or at a rate that may be a function of other variables or other parameters. The network of transitions between all identified states gives rise (in the simplest case) to a matrix of first-order linear differential equations which are directly soluble. Typically, in infectious disease modelling, at least one of the transitions gives rise to non-linear equations because the rate of cross-infection depends upon the number of carriers. Thus EPIMOD allows for solution of non-linear problems by incorporating a general package for the solution of differential equations and by using the SEARCH algorithm of Ken Lange to find the maximum likelihood solution.



A key feature of the package is that the front-end user can conceptualise the model simply in terms of a flowchart of biological states and transitions, and does not even have to see the underlying differential equations. Model usage, and the steps needed to

connect data to the model, are menu-driven. Output is provided interactively, with the parameter estimates and standard errors, the overall goodness of fit, as measured by the likelihood, and tables of observed and fitted numbers in appropriate cases. The user can specify states which are not separately observable; for example, in modelling longitudinal bacterial carriage, a particular swab might be negative either because it was a true negative (*ie.* swab well taken, but no pathogen present) or because it was a false negative (*ie.* pathogen present, but missed because of a poor sample). For any particular swab, we cannot decide between these two possibilities. However, by allowing for the possibility of a false negative, the data and the other modelling assumptions will allow an estimate of the false negative rate to be made.

Other features of the package include :

1. A simulation or "what if" option. Because a key objective of the modelling is not only to understand the status quo, but to look for the most effective interventions, the package allows for the structure and parameter estimates from a model to be stored, and to provide the basis for a simulation of what would happen if the value of one of the key parameters was changed by an intervention.
2. Data loading, data transformation and error checking functions.
3. Constraint and functional dependence capability for the parameters to be estimated.
4. Housekeeping functions to control the activity of the system, carry out statistical tests, store models etc.

Modelling of Onset of Ear Infections (Otitis Media)

In collaboration with Amanda Leach and other members of the Ear Health Unit, epidemiological models have been fitted to the onset of otitis media (OM) which affects 50% of Aboriginal infants in our longitudinal study within one month of birth. Most importantly, we found that the rate of onset of OM (16% per day) was greatly increased in infants already colonised in the nose and throat with harmful bacteria; the rate was only 2% per day in those without such bacterial infection [102]. These findings provide a strong rationale for social and environmental programs to reduce overcrowding and to improve hygiene and reduce rates of cross-infection. They also provide an important rationale for our ongoing trials of antibiotic treatment from an early age.

Endemicity of Respiratory Bacteria

Amanda Leach, Heidi Smith-Vaughan, Kath Kemp, Dave Kemp, Terry Nienhuys, Peter Morris, John Mathews

Most rural Aboriginal infants are infected with *S. pneumoniae* and with *H. influenzae* within one or two months of birth, and carry multiple strains concurrently until the age of 7-10 years [102, 176, 197, 259, 298, 313, 365]. The chronicity of nasopharyngeal carriage, which leads to high rates of otitis media (see **Figure 3** and Ear Health and Education Unit report) and respiratory infection, appears to be due to a multiplicity of factors (**Figure 3**), probably including the queueing of large number of immunologically distinct strains, early age of infection, and poor immune responses.

EPIMOD has been used to estimate the mean carriage times of different serotypes of pneumococci (**Table 3**) using a model that allows for interrupted periods of carriage as the dominant strain.

Table 3 : Mean Carriage time (Days) for Selected Pneumococcal Serotypes

Serotype	Mean Carriage Time*
19A	183
16	136
9V	152
23F	154

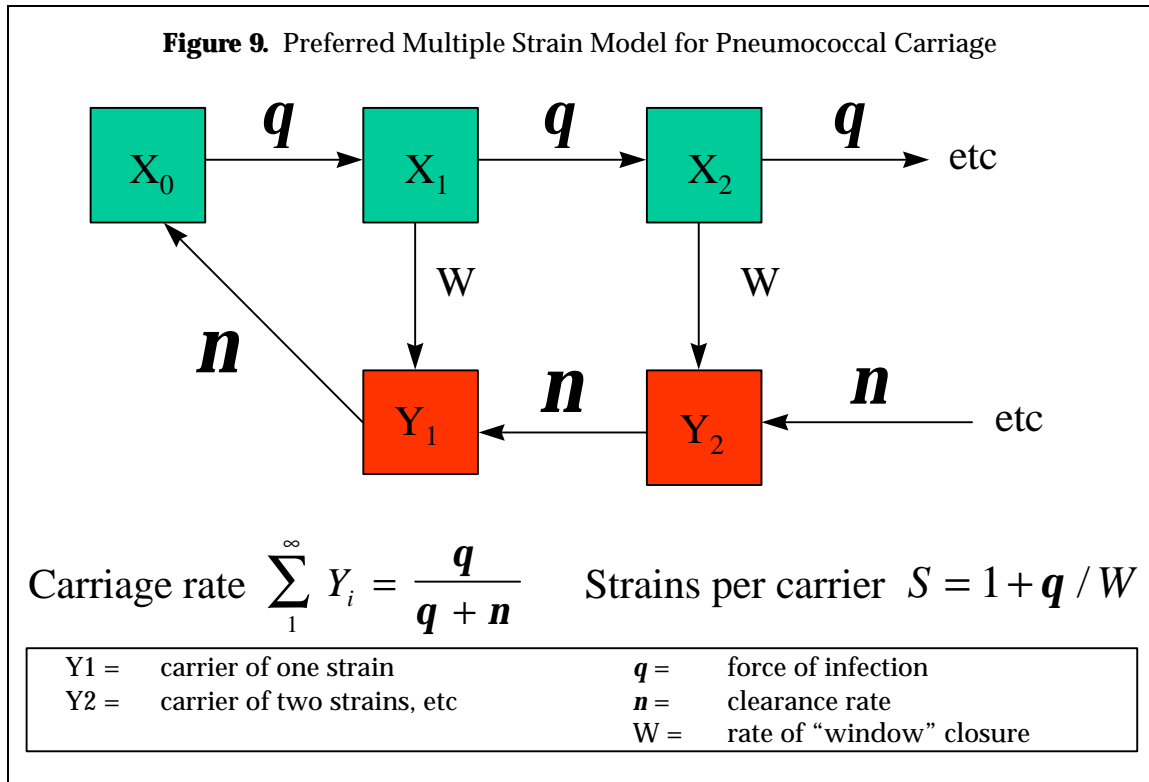
* as dominant serotype, allowing for interrupted periods of carriage

EPIMOD has also been used to estimate the aggregate force of infection for infants and children and adults exposed to multiple strains of pneumococci. The largest estimate is for infants in the highlands of New Guinea (24 exposures per year), compared with a rate of 12 per year for children in a desert Aboriginal community, 3 per year for children in child-care in Darwin, and <0.3 per year for “only” children living at home in Darwin and not in child care. The highest documented rate in a developed country was 6 exposures per year for US recruits in an Army camp in World War 2.

Model for Multiple Strain Carriage in Endemic Populations

Overcrowded populations in poor social circumstances have high forces of infection and high rates of carriage of pneumococcus, haemophilus and other respiratory bacteria. Such endemicity is characterised by carriage of multiple strains of each species through infancy and childhood. A notable feature of such endemicity is that when the force of infection is higher than the average clearance rate for each strain, there is a potential for concurrent carriage of multiple strains of the same species in an individual host. Indeed, concurrent carriage of multiple strains of pneumococcus and haemophilus is commonly observed, but because of competition between strains, the number of strains carried is less than might be estimated from the aggregate force of infection and the clearance rates. John Mathews has evaluated simple models to explain the apparent stability of endemic carriage of large numbers of strains in small populations as well as the observed [179, 259, 298] frequency of carriage of multiple strains. These models take account of the host immune response and of competition between strains, and derive formulae to explain the characteristic age-dependence of different strains of pneumococci, and the concurrent carriage and queuing of multiple strains in the same individual. A strong assumption of the preferred model (Figure 9) is that when multiple strains are carried, they are cleared serially, rather than in parallel. As a consequence, each strain can minimise its rate of effective clearance while “hidden” from the immune response, and maximise transmission to a new host when it takes its turn as the dominant strain. This minimises the competitive evolutionary cost to individual strains as the periods of hidden carriage make each strain less liable to stochastic elimination in small population isolates. Thus the effects of competition between strains appear to be partly offset by cooperative consequences of their interactions with each other and with the immune system.

Figure 9. Preferred Multiple Strain Model for Pneumococcal Carriage



The model also has contemporary and practical relevance : for example, although any antibiotic resistant strain will increase in frequency while antibiotics are in use, the rapid reduction in frequency of resistant phenotypes when antibiotic use ceases [eg. 298] is explained by competition between strains in endemic situations. Another prediction is that with minimal cross-reactivity between different pneumococcal serotypes, conjugate pneumococcal vaccines will lead to the replacement of vaccine-strains by non-vaccine strains in endemic populations. Another important feature of the model is that it can explain why some pneumococcal serotypes are “paediatric” while others are “adult”. Paediatric serotypes are characterised by an early age of infection because their rate of clearance is less (eg. 2.5 per year) than the rate of clearance for adult strains (eg. 4 per year). With a slower rate of clearance, paediatric strains are carried for longer, they have a higher carriage prevalence, thus a higher strain-specific force of infection, and thus an earlier mean age of infection as “paediatric” strains. For adult strains, the clearance rate is greater, leading by a complementary chain of reasoning, to a later (adult) mean age of infection or carriage.

For Group A streptococci, modelling results are consistent with considerable cross-reactivity between strains, implying that a successful vaccine would not necessarily lead to replacement of vaccine strains by non-vaccine strains. The overall modelling framework will help guide vaccine development and use, help with interventions to minimise infection in child-care centres and other overcrowded circumstances and guide strategies to optimise antibiotic treatment in the face of antibiotic resistance. A manuscript is available.

Endemic Model for *C. pneumoniae*

Sue Hutton, Val Asche, Fiona Douglas, Heather Dodd, Dave Kemp, John Mathews

C. pneumoniae is characterised by short-lived immunity and recurrent infection. Infection is endemic in Aboriginal communities, whereas in more affluent urban populations, there may be a more epidemic mode of spread, with inter-epidemic periods. For example,

seroprevalence and incidence data from Seattle suggest that the mean rate of infection is $10.5 \pm 0.6\% \text{ y}^{-1}$, whereas our Aboriginal data lead to an estimate of $50.4 \pm 4.2\% \text{ y}^{-1}$, both on the assumption that IgG seroconversion requires at least two exposures (**Figure 8**). Furthermore, IgG antibody responses in Seattle are much more persistent (a half life of 18 years after the second exposure) than in the Aboriginal population (a half life of 2 years). This difference could be a consequence of the earlier age of first exposure in the Aboriginal population, or of poor nutrition, or be related to the presence of other chlamydial species or serotypes in the Aboriginal population.

The waning of immunity adds to the pool of susceptibles, and together with the high rate of cross infection, helps to maintain endemicity of *C. pneumoniae* in Aboriginal and other disadvantaged populations. Latent infection with reactivation could also contribute to endemicity.

Models for Age Distribution of Post-Infective Disease

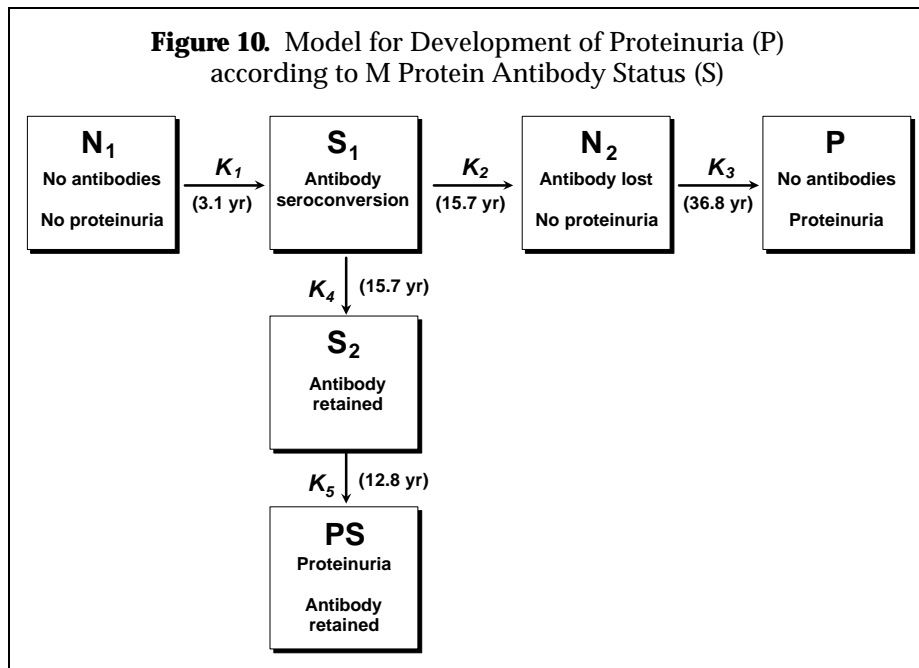
John Mathews, Jonathan Carapetis, Bart Currie, Peter Morris, Don Gardiner, KS Sriprakash

In an endemic situation, any disease caused by (first) exposure alone would have an age-specific incidence with an approximately negative exponential distribution. This is rarely observed. A close approximation is provided by Kawasaki Disease (KD), presumptively due to the first exposure to a toxin-producing staphylococcus or streptococcus, where the negative exponential is presumed to be modified by the protective effect of maternal antibodies in early life. A model incorporating these assumptions can explain the age specific incidence of KD in all populations for which data are available (**Figure 6**).

The age distribution of rheumatic fever (RF) also suggests that it does not behave as if caused by the first exposure to a rheumatogenic strain of GAS. In different populations and eras, the peak incidence of RF has occurred at ages from 8 to 12, with an earlier onset in populations with higher incidences of Group A Streptococcal (GAS) infection and RF. However, although the age of peak incidence varies, the shape of the age-specific incidence curve is totally inconsistent with RF being caused by a simple "one-exposure" model. Rather it is consistent with a multi-stage model (possibly three stages). We suggest that all three stages reflect separate exposures to GAS, and that RF is induced after the third event, provided that an endogenous process of "desensitisation" has not intervened. Such a model can explain many of the epidemiological features of RF, including the rate of relapse in subjects not receiving prophylaxis. Furthermore, it provides a new frame of reference to help test immunological models of RF pathogenesis.

Proteinuria has an Earlier Age of Onset in those with GAS Antibodies

In collaboration with Alison Goodfellow, Wendy Hoy and others, we modelled the distribution of proteinuria and antibodies to M-protein in Tiwi children and adults. The model (**Figure 10**) suggested that all subjects probably seroconverted in childhood, and that proteinuria (an early sign of renal disease) developed more quickly (mean age of proteinuria onset = 31.6 yr) in those who remained seropositive, possibly because of repeated infection, than in those who became seronegative (mean age of proteinuria onset = 55.9 yr). The effect of seropositivity was greatest in those who were obese as adults, although obesity was independent of serological status. These results strongly suggest that renal disease is driven both by (GAS) infection and by metabolic factors in Aboriginal people on the Tiwi Islands [350].



THE NUSA TENGGARA TIMUR PROJECT

Mary Dorling examined the sex industry in Kupang, East Timor, with the aim of understanding its organisation and structure, and the contexts leading to risk behaviours for sexually transmitted diseases and HIV infection.

The study revealed two distinct and quite specifically defined populations involved in the industry in Kupang. The organisation, management, structure and features of the sex industry are quite separate for each group. Perhaps the most significant feature of the research, and one that is implicated in perceptions of risk, has been in understanding how accusations of blame which indict the 'other' affect both populations. In the population that does the blaming a sense of their own invulnerability is induced and, in the population that is blamed, a sense of their vulnerability. These do not exist in isolation and both are reinforced and/or mitigated by extant social factors, particularly those relevant to locations that are geopolitically peripheral such as Kupang. This aspect of the research has wider applications and provides some understanding of how and why so many population groups, including our own, resort to blaming "over there" for the ill.

The knowledge gained in the study about how people think about concepts such as health and illness in cross-cultural situations was also revealing, specifically that it is not so much the information that is provided for people but how they process it that is important. This has very important implications, for self-medication, self-diagnosis of disease and the practice of preventive behaviours. All of these factors have great significance in economically poor areas such as Kupang where dual medical systems exist, where treatment is often scarce and expensive and the "magic bullet" (antibiotic) is so freely available and is combined with traditional medicine regimes to effect self constructed concepts of "good health" and cure from disease.

OTHER WORK

Dorothy Mackerras was part of a successful multi-institution group, including marine biologists and nutritional toxicologists, who won the tender to investigate the allegation



that there was a leak of diesel from an underground storage site on Groote Eylandt and determine whether there was any risk to human health. A survey of Aboriginal and non-Indigenous inhabitants was done to determine the frequency and amount of seafood consumed from the designated target area. Other members of the group analysed sea water, collected identified species from the area and tested them for designated hydrocarbon content. Analyses revealed that there was a leak of diesel, but it was not present in the fish. Hydrocarbons were detected in oysters, however there were so few oysters in the area that no-one could receive an excessive chronic dose. She also contributed several chapters to the recent Australian textbook on public health methods [369-374].

PUBLIC HEALTH EDUCATION

Dr Antonia Bagshawe joined the School in 1993 as Coordinator for the Master of Public Health coursework in the School accredited by the University of Sydney. The units offered through the School have helped to channel the research findings of the School into the education and service sectors, and staff from health service organisations have been involved both as students and teachers on the course. More recently, the public health coursework has been accredited by Northern Territory University, and some units may be offered, on a cooperative basis, to students enrolled with other institutions. Academic teaching in public health will also be linked to health education programs in schools and to programs for the wider community.

Dr Bagshawe moved to Alice Springs in 1995 and continued as Coordinator of the coursework until she resigned to move to Perth at the end of 1997. Dr Ross Bailie, from NCEPH, joined the School to coordinate an expanded teaching program from 1998. More details are given in the *Education & Training* section of this report.

Renal Unit

Wendy Hoy

The Renal Program was established in 1992 to better understand the problems that underlie the increase in renal failure among NT Aboriginal people. We have tracked the development of this epidemic and have established that the underlying renal disease arises out of a menu of several risk factors, which include the metabolic and haemodynamic changes that accompany increasing adult weight, infections, heavy drinking, and intrauterine and infant malnutrition. We have preliminary data that such early malnutrition impairs the development of the kidneys, which are consequently smaller than normal. We have defined the extraordinary enlargement of the glomeruli (filtering units of the kidney) that marks the excess susceptibility to kidney disease, and have begun to study its causes in a program that has been extended to other indigenous populations internationally. Our data suggest that the links between kidney disease and cardiovascular disease are very powerful indeed, and we are developing this important theme further.

We have also designed and implemented a program to treat Tiwi people at risk for kidney failure and cardiovascular disease. After two years of treatment blood pressure levels are much lower and the kidney disease has been slowed down dramatically. The program has also created an environment conducive to the delivery of health messages, and people are slowly adopting lifestyle changes. All these projects provide solid frameworks for future work.

EDUCATION AND SERVICE PROVISION

Team members have presented our findings and the attendant health messages they imply to several remote Aboriginal communities, including all the Tiwi communities and Oenpelli and Galiwinku. They have also been shared with the Darwin-based Aboriginal Health Services Danila Dilba and Bagot community, with community development courses at Nungalinga College, and the Health Worker training Courses at Batchelor College, and to working parties on Renal Disease in Nhulunbuy, Katherine and Alice Springs. We have developed guidelines for the screening and treatment of chronic disease in Aboriginal people in the Top End, participated in the development of the NT Renal Strategy, reported to the Public Accounts Committee of the NT Legislature, participated in the NHMRC's working parties on "Provision of end stage renal disease treatment in remote areas" and "Development of national guidelines for diagnosis and treatment of diabetes and renal disease in Aboriginal and Torres Strait Islanders", participated in the Queensland and Torres Strait Island Diabetes Strategy, and the development of the National Diabetes Strategy. Various team members have presented widely nationwide, and provided the largest body of input at the first-ever conference on Renal Disease in Indigenous Populations, in conjunction

with the International Society of Nephrology meetings, in May 1997, and we have presented our findings in New Zealand, the United States and in Denmark.

END STAGE RENAL REGISTRY (ESRD)

We have collated and reported the ESRD experience of Aboriginal people in the Top End, resulting in 2 publications and several working documents. The data provide information which should guide health care planning and resource allocation, and against which to compare future trends and the efficacy of interventions.

Ms Judy You (Menzies MPH scholarship in our Unit) is defining the true cost of maintaining a person on dialysis in the Top End, with Ms Carol Beaver from the Health Economics Section of Territory Health Services as co-supervisor. Such a project has not been undertaken to date. It is anticipated that the costs will be very high, especially in Aboriginal people, who are sicker, and consume more resources, both in terms of health care services, and through indirect costs associated with relocation from their remote communities.

THE COMMUNITY STUDY OF THE EPIDEMIOLOGY OF RENAL DISEASE

We have screened 1400 residents of the Tiwi islands for kidney disease and its associated conditions, and conducted repeat evaluations through late 1997. This program started in mid 1992, supported by two grants from the NHMRC, the Stanley Tipiloura Fund and the Australian Kidney Foundation. We are indebted to the commitment and driving force of Bev Hayhurst and support from AHWs Nellie Punguatji, Jerome Kerinaia, and Eric Tipiloura for the success of this project. Dr David Pugsley (Adelaide) and Dr David McCredie (Melbourne) advised and assisted with many aspects of the study. Baseline data show that kidney disease, which affects more than half the adult population, is multifactorial. Risk factors include infected skin sores and scabies, low birth weight and infant malnutrition, increasing weight gain in adolescence and adult life, insulin resistance, diabetes, rising blood pressures, heavy drinking and in women, repeated pregnancies. Megan Rees (BMedSci, 1994) and Emma Kile (BMedSci, 1995) helped define the role of low birth weight in renal disease, while Kate Walker (BMedSci, 1996) showed the additional links of renal disease to infant malnutrition and to skin infections and poststreptococcal glomerulonephritis. Serologic studies in the MSHR labs (Dr Alison Goodfellow) suggest that persistent memory of streptococcal infection is correlated with renal disease in this group. Dr Andrew White, paediatrician and PhD student (Australian Kidney Foundation Scholarship) is further evaluating these clinical and serologic associations. Members of our unit have developed health education packages related to these findings. Interesting ACE allele data, done by Siannah Papodopoulos in the laboratory of Dr George Jerums at the Austin Hospital, will be further pursued by Dr Stephen MacDonald as part of his PhD project.

We are now describing the natural history of renal disease in this community, the strong links between cardiovascular and renal disease, (Dr Stephen MacDonald, PhD student, NHMRC scholarship) and using the findings to advocate for better intersectoral and services for Aboriginal people to address the broad menu of preventable risk factors identified here.

FAMILY HISTORY STUDY

The objective of this program, supported by an NHMRC grant, and started in 1994, is to define the extent of family clustering of renal disease and begin to understand its basis. Prof John Mathews is the Chief Investigator and Dr Simon Foote (Walter and Eliza Hall Institute), the Molecular Biologist, while Bev Hayhurst has led the field work and Jerome Kerinaia and Nellie Punguatji have been community liaisons. Family pedigrees have been drawn up, and given back to the Tiwi people. Blood samples are to undergo genetic studies by Simon Foote and this data will be linked to clinical evidence of renal disease, diabetes and hypertension. A poster by Bev, Jerome and Nellie, presented at the XIVth International Congress of Nephrology at Yulara, 1997 won the best and most original poster award. We hope to expand this study to embrace other potential markers of high risk for metabolic/renal and cardiovascular disease, and the opportunities for international collaboration are exciting.

RENAL ULTRASOUND STUDY

Our studies on the Tiwi Islands show a clear correlation between kidney disease and low birth weight. We propose that early malnutrition results in underdeveloped (small) kidneys which are then at higher risk for the development and progression of serious kidney disease. In 1997, Janine Spencer, Australian Kidney Foundation Research Fellow, began a community-based ultrasound study of renal volume in school-aged Tiwi children, and has defined a smaller than average kidney length than in non-Aboriginal standards, and even lower volumes in Tiwi children who were low birth weight. Dr Gurmeet Singh and Dr Andrew White (PhD students with scholarships from the Australian Kidney Foundation and the Children's Hospital in Sydney) will continue these studies, and extend them to younger children and to adults as well

THE RENAL AND CARDIOVASCULAR-PROTECTIVE TREATMENT PROGRAM

With the support of Servier Australia, and the Australian Kidney Foundation, we have designed a program to treat the high burden of chronic disease uncovered in the Tiwi screening program, using the long acting angiotensin converting enzyme inhibitor, perindopril (Coversyl, Servier) as the primary pharmacologic agent. Team members are Jerome Kerinaia (until March 98), Nellie Punguatji, Eric and Elizabeth Tipiloura, Angela Kelly, Kiernan McKendry and Susan Jacups (until June 98). The program has enjoyed great acceptance. Two hundred and twenty adults, or a quarter of the adult population, have qualified for and begun treatment. Two hundred people have completed one year of therapy and 100 have completed 2 years. At both these intervals, there has been a dramatic lowering of blood pressure, stabilisation of albuminuria, which reflects the presence and severity of renal disease, and the progressive loss of renal function in the group as a whole has been aborted. We anticipate this will result in a great reduction in the number of people progressing to renal failure and, more important, at least a 40% reduction in heart attack and stroke. If the momentum can be maintained, an increase in average age of death of adults should soon be apparent. The program provides a model for chronic disease management in Aboriginal adults, and interest is increasing around Australia and in other countries with similar health problems.

EVALUATION OF THE TREATMENT PROGRAM

Philip Baker (PhD student, NHMRC scholarship) is undertaking a study of "*An economic evaluation of the screening and treatment of renal disease in Australian Aborigines*". The analysis will be taken from a societal perspective evaluating the effectiveness of the treatment program

in persons at risk for progressive renal and cardiovascular disease. Cost-effectiveness studies are particularly useful to health policy makers and fund holders as they can identify the best-buys for health. Estimates of program effectiveness are modelled using the rates of progression in the natural history and the alteration in disease progression achieved in the treatment program. Key to assumption of cost-effectiveness is that of good compliance. Angela Kelly, research nurse with the treatment program, is examining reasons for the good compliance and effectiveness observed over the past 2 years of the program. She will be offering suggestions on the how success can be achieved in other communities where the program may be implemented.

EVALUATION OF RENAL MORPHOLOGY AND GLOMERULAR SIZE AND NUMBERS

In collaboration with Dr Diane Howard at the Royal Darwin Hospital, we described the glomerulomegaly (large filters) that marks the excess risk of Aboriginal people to renal disease. This was later quantitated, and found to be pronounced, in the laboratory of Dr John Bertram at Melbourne University. We have undertaken a multicentre biopsy study to evaluate the applicability of these findings to other populations. We propose that glomerulomegaly might represent compensatory enlargement due to underendowment of glomerular numbers related to early malnutrition, and will further evaluate the hypothesis by sizing and counting glomeruli in a prospective multicentre autopsy study. Professor Michael Hughson in Jackson, Mississippi, Prof Kincaid-Smith, Dr Tony Seymour and Dr John Bertram are all participating in these studies, which are coordinated by our Unit. Renal biopsies will be analysed for glomerular volume and numbers. This work has been supported by grants from the Australian Kidney Foundation and from Janssen Cilag, and will be the prime focus of Dr Alan Cass, Nephrologist, PhD student, (Scholarship from the Children's Hospital in Sydney).

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(Refereed and Otherwise)
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