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From the Editor: **Research Overview**

Medical research is one of the cornerstones of the modern teaching hospital. Concord Hospital has a proud record of medical and scientific research, and is committed to nurturing an environment that will deliver research of excellence into the 21st century.

Research at Concord Hospital has brought together the best and most needed multidisciplinary clinical and biomedical research that will improve our understanding of health in later life. Through close association with The University of Sydney and the ANZAC Research Institute, studies into fundamental processes of ageing and diseases that accompany ageing have been established and the scope of this research continues to grow.

By 2030 it is expected there will be over 1.2 billion people aged over 60 in the world and a large fraction of these individuals will be over the age of 80. It is therefore increasingly apparent that the emphasis of research in diseases and conditions of ageing is crucial as more people become at risk of developing degenerative diseases, frailty and dependence that will accompany our ageing population.

As editor, I feel privileged to be showcasing the diverse spectrum of research being undertaken by our talented and dedicated staff. The striking features that exemplify Concord Hospital’s commitment to research are the foresight to continually recruit research of excellence and to nurture close collaboration across the existing multiple disciplines. This has focused the aims of our research to a common goal of extending healthy life and working towards treatments and possible cures for diseases and conditions associated with ageing while maintaining the highest standards of clinical medicine and patient care.

Dr Marina Kennerson  
Senior Scientific Officer  
(Molecular Medicine and Northcott Neuroscience Laboratory)  
Editor, Research Report
Message from the Chair of the Concord Hospital Research Committee

It gives me great pleasure to see the second biennial Concord Hospital Research Report published, with this issue focusing on research on ageing. I would like to thank Dr Marina Kennerson and Ms Virginia Turner for their hard work in planning, collating and editing the material, and the many researchers who contributed to this report.

Ageing will be the major health problem for the next 20-50 years and is seen as a research priority by Federal and State governments. It is also one of the major research themes of the College of Health Sciences and Faculty of Medicine of the University of Sydney, with Concord Hospital taking the lead role in this theme at the University. As will be obvious from reading this report, we are well positioned to have a major impact on research in this area at a national and international level. The Anzac Research Institute with its primary theme of ageing is now well established at Concord, and in just a few years has been able to virtually completely fill its laboratories with active researchers. There are now over 30 postgraduate research students at Concord, and a number of postdoctoral scientists have taken up positions in the Anzac. The traditional focus on ageing led by CERA (Centre for Education and Research on Ageing) has been augmented by a number of new initiatives:

- NHMRC-funded CHAMP study (Concord Health and Ageing Male Project, Principal Investigator: Professor Bob Cumming) will be the world’s largest cohort study of older men. This $1.7 million 5 year study will focus on men’s health, quality of life and survival and their determinants using the population living in and around Concord.
- ARC-NHMRC Research Network in Ageing Well (Principal Investigator: Professor Hal Kendig). This network funded for $2.5 million over 5 years will operate from the Concord campus to support high quality interdisciplinary research in the National Research Priority Goal of “Ageing Well, Ageing Productively”.
- A new Chair in Geriatric Pharmacy has been established at Concord.

This publication showcases research at Concord on many fronts, ranging from direct patient care to laboratory-based molecular and genetic determinants of disease. Research at Concord is multidisciplinary and involves nurses, physiotherapists, dieticians, speech therapists and pharmacists in addition to physicians, surgeons and laboratory scientists. We have highlighted the work of some of these researchers in this report.

Research in a major teaching hospital like Concord is part of our mission statement – it has a fundamental role in improving healthcare through a better understanding of disease. I hope that by increasing awareness of research activity at Concord through this publication, the research effort here will receive the recognition and support from the community it deserves.

Professor Ben Freedman
Chair, Concord Hospital Research Committee
Message from the Chair of the Concord Hospital Human Research Ethics Committee (HREC)

The 2004/2005 Research Report gives me the opportunity to thank a number of people who contribute to the work of the Concord Hospital Human Research Ethics Committee (HREC).

I would like to acknowledge all the members of the HREC who give their time and intellectual input freely in order to help the hospital and its researchers deliver quality research. My thanks also to Ross Bradbury and the Hospital Drug Committee for providing scientific review of many of the research applications.

The past two years have seen a number of changes in both State and Commonwealth legislation, which have affected the work of HRECs. This has led to requirements for increased governance and oversight by HRECs in the areas of privacy, human tissue research and radiation exposure to research participants.

The Ethics Branch of NSW Health has been instrumental in developing changes to the way that ethical review of multi-site research will be handled in the future. It is anticipated that by July 2006, any research application submitted to more than one HREC in NSW would only require review by one “lead” HREC. Other HRECs involved would be required to “sign off” without change. This will hopefully help to reduce much of the duplication associated with multi-site review.

We are still waiting for a national ethics application form that will further help to reduce duplication.

Issues of concern for the Concord Research Office and Pharmacy Departments have included difficulty in finding enough scientific reviewers for new research applications; increasing workload requirements; indemnity and legal oversight governance and increasing complexity of trials.

Membership of an HREC is entirely voluntary and is not remunerated. Training of members of HRECs has received a boost in the last two years with a number of seminars and conferences organised by NSW Health and by the Australian Health Ethics Committee (AHEC). The standard of knowledge and level of competency required by HRECs and their members will be areas of increased scrutiny over the next decade. Similarly for researchers, the level of knowledge of the ethical process, governance and legal framework we operate in, will become just as important as having an understanding of statistics and scientific methodology.

Finally I want to acknowledge and sincerely thank our Executive Officer, Ms Virginia Turner and her assistant Mr Rodger Lomberg.

Dr Garry Pearce
Chair, Concord Hospital Human Research Ethics Committee.
In February 2005 Professor Hal Kendig took up a joint appointment as Research Professor of Ageing and Health at the University of Sydney and as National Convenor of the ARC/NHMRC Research Network in Ageing Well. As Research Professor in the Faculty of Health Sciences he also serves as Chair of the College Research Program in Ageing and Health.

This work at Concord - in association with the Centre for Education and Research on Ageing (CERA) – aims to advance collaborative research addressing the ageing of Australia over coming decades.

After completing his PhD in ageing research at the University of Southern California in 1975, Hal held several appointments in the Research School of Social Sciences at the Australian National University, where he led the Ageing and the Family Project. From 1989 to 1997 he served as Director of the Australian Research Council (ARC) Key Centre in Gerontology at La Trobe University and in 1998 he commenced as Dean of the Faculty of Health Sciences at the University of Sydney.

Professor Kendig has published widely on social, health, and policy aspects of ageing in Australia and internationally. Drawing on both survey research and qualitative studies, he and his colleagues have demonstrated the importance and complexities of family life of older Australians, provided an evidence base to inform aged care policy development, and identified ways in which health-promoting life styles can improve the independence and quality of older people. He has more than 170 publications, including 14 books, and he contributes regularly to policy development and public debate concerning ageing. His current research includes the 11-year Melbourne Longitudinal Surveys of Healthy Ageing.

The ARC/NHMRC Research Network on Ageing Well was awarded a grant of $2.5m over the next five years to foster multi-disciplinary research of national and international significance. The Network of six universities and 50 participants aims to increase the scale and quality of multi-disciplinary ageing research, and to enhance research capacities especially for emerging researchers (www.ageingwell.edu.au). It focuses on the 2003 National Research Priority Goal of ‘Ageing Well, Ageing Productively’ to develop better social, medical and population health strategies to improve the mental and physical capacities of ageing people. The Network will also help build better bridges between researchers, governments, and consumer groups.
Dr Sumana Gopinath
Neurologist and PhD candidate

Dr Sumana Gopinath is a neurologist, currently in her third year of PhD candidature at the ANZAC Research Institute.

Sumana moved to Sydney in 1992 after graduating in medicine and surgery at the University of Madras, India. She continued training in medicine at St.Vincents Hospital and Westmead Hospital, Sydney and subsequently underwent training in neurology at Liverpool and Westmead Hospitals, Sydney. She became a Fellow of the Royal Australian College of Physicians (Neurology) in 2002.

In 2003, she commenced her research in the field of neurogenetics under the supervision of Professor Garth Nicholson and Dr Marina Kennerson at the Northcott Neuroscience Laboratory, ANZAC Research Institute.

Sumana’s research studies the genetic causes of disorders affecting motor neurons.

Motor neurons are nerve cells that carry impulses from the central nervous system to activate muscles. Some disorders that affect motor neurons are caused by mutations in genes. Gene mutations affecting motor neurons can cause severe, debilitating, rapidly fatal conditions like amyotrophic lateral sclerosis (ALS) or milder forms of disease like hereditary motor neuropathies which do not affect survival. Work at the Neuroscience Laboratory aims to find new, unknown genes that affect motor neuron function. Studying such genes would help in the development of therapies for disorders like ALS.

Sumana’s work has been supported by a University of Sydney post-graduate award. She has been awarded the Nina Buscombe award 2005 by the Motor Neuron Disease (MND) Association of Victoria to attend the 16th International Symposium on ALS/MND being held in Dublin, Ireland in December 2005, and has been awarded a conference support grant by the Post-graduate Research Support Scheme (PRSS), University of Sydney.
Between 2002 and 2005 George Lau was a Research Fellow of the Department of Cardiology at Concord Hospital. He has recently moved to the United States for a 2-year post-doctoral fellowship in cardiology at Massachusetts General Hospital, Boston.

George Lau graduated from the University of Sydney in 1994 and became a Fellow of the Royal Australasian College of Physicians in 2001. In 2002 he was appointed as research fellow and PhD student in Medicine, in the Department of Cardiology Concord Hospital under the supervision of Associate Professor Len Kritharides from Cardiology and Dr Lloyd Ridley of the Department of Radiology. George was Clinical Superintendent of Medicine at Concord Hospital in 2002, and between 2003 and 2004 was a member of the Concord Hospital Human Research Ethics Committee.

George’s work has been recognised by a number of prestigious awards. In 2003, he was awarded a Pfizer Cardiovascular Lipid Research Grant ($55,000) to conduct his work on minimally-invasive detection of hyperplasia in vein grafts after coronary artery bypass graft (CABG) surgery. He was recently awarded the Ophelia Ann and Rose Hilda Lord Postgraduate Research Scholarship ($28,188 per annum) by the National Heart Foundation of Australia for 2004-2005.

The disease processes that affect vein and artery grafts in the first year are thrombosis and intimal hyperplasia (thickening of the vessel wall). The risk factors for graft disease are poorly defined, particularly in relation to diabetes, even though it is known that diabetics have a worse prognosis than non-diabetics post-bypass.

George developed a reproducible, minimally-invasive method to assess graft wall thickness (a measure of intimal hyperplasia) using computer tomography. This has allowed assessment of the natural progression of graft disease in diabetic and non-diabetic patients, and to relate this to diabetes and a range of other candidate risk factors (smoking, blood pressure, medications etc).

Early results of the research have shown that high levels of triglycerides in the blood are associated with early occlusion of radial artery bypass grafts in particular. The researchers have also found that early saphenous vein graft wall thickness is greater in diabetic than in non-diabetic patients.

The assessment of risk factors in coronary bypass grafts surgery
Dr Lau has studied patients who undergo coronary artery bypass grafting. In the first year following CABG surgery there is a significant failure of the grafts in about 15% of cases.
In late 2003, Dr Paul Witting joined the newly formed Vascular Biology Group at the ANZAC Research Institute as Senior Scientist. He has also been appointed as Senior Lecturer (Research Only) at the University of Sydney. Since arriving he has been successful in gaining over $190,000 in equipment grants to establish the research group.

Paul was awarded his PhD in 1994 by the University of Sydney where he trained as an analytical chemist with a general interest in biochemistry. He has completed post-doctoral appointments at The Heart Research Institute, Sydney (1994-1999) and at the University of British Columbia, Canada (1999-2001). The latter was financed by a competitively funded National Heart Foundation Fellowship. Paul is a career researcher funded currently by an Australian Research Council (ARC) Fellowship (2003-2007).

Paul's relocation to Concord Hospital was designed to give him an opportunity to work closely with clinicians such as cardiologists and neurologists, and to further his research exploring a pathological role for oxidative stress in diseases associated with vascular dysfunction (such as atherosclerosis, heart muscle dysfunction and stroke).

Over 48,000 strokes occur in Australia every year with a stroke occurring every 11 minutes. The ageing demographic within Australia combined with the established increased risk of stroke with age indicates that the numbers of people suffering from stroke will likely rise (reportedly to 74,000 by the year 2017 if preventive therapies are not developed to inhibit this disease). Stroke and TIA are potentially costly disorders - in Australia it is estimated that stroke accounts for 4% of the total health costs for all diseases combined.

During a stroke, brain cells are exposed to hypoxic conditions (conditions where there is a reduced availability of oxygen to the brain) and this would normally result in a significant proportion of brain cells (neurons) dying. At this time, there is no accepted medical treatment that will inhibit or repair the damage that occurs to neuronal cells in the brain as a result of the hypoxia-reoxygenation injury sustained during the stroke. Therefore, the development of therapeutic drugs targeting people identified as being susceptible to, or recovering from, stroke is keenly sought.

With this background in mind, one of Paul’s research aims is to test a synthetic antioxidant called Bisphenol, which is known to decrease oxidative stress in vivo. Notably, Bisphenol is able to pass the blood brain barrier and therefore has a potential neuroprotective effect. Paul’s work investigating cellular and animal models of stroke is described in more detail on page 22.
Dr Sharyn Kelleher - Nurse Researcher

Sharyn Kelleher is a career nurse working in the Department of Andrology as a Clinical Nurse Specialist (CNS).

After completing hospital based nursing training in 1985, Sharyn worked in acute care areas culminating in an Intensive Care Certificate at the Royal Prince Alfred Hospital in 1993, for which she was awarded the hospital’s academic prize. She then worked as a Nurse Manager in a High Dependency unit and in 1996 completed a Graduate Diploma in Nursing Management.

Realising that her forte was in clinical research and education, she applied for a nursing position in 1997 in the Department of Andrology. She has worked in the Andrology Department for over eight years and early on realised that this area of nursing was her vocation. Within one year of starting in the department she presented research at the yearly conference for the Australian Endocrine Society. In 1999 she was awarded a travel scholarship from the Endocrine Nurses Society of Australia to present her research in Toronto, Canada. Since then Sharyn has completed a Doctor of Philosophy (Medicine) in Andrology, and continues her clinical work and research in this area for the betterment of men affected by all types of andrology-related disorders.

Androgen deficiency (AD) is the most common hormone deficiency in men. Although there are no official figures available, the prevalence of AD in the wider community is estimated to be around 1:200 men. Men who have AD require life-long androgen replacement to maintain their bones, muscles, normal mood, energy and libido and secondary sex characteristics.

Unlike oestrogen replacement in women, which is managed with oral medication, male hormone replacement is made more challenging due to the low oral bioavailability and short circulating half-life of testosterone.

Other routes of administration have therefore been sought. In Australia, oral medication, topical patches, oil-based injections and testosterone pellet implants (the surgical insertion of small pellets of testosterone under the skin of the abdomen) are available. However, none of these androgen replacement therapies are without their drawbacks.

Testosterone pellet implants were the focus of Sharyn’s PhD thesis. The implants are convenient and effective, but a pellet may be extruded after approximately 10 percent of procedures. Extrusion occurs when one or more of the implanted pellets tunnels its way back along the subdermal track and is extruded back through the skin, usually from the insertion site. Sharyn’s PhD project consisted of a series of randomised controlled clinical trials that sought to determine whether alteration to the implantation procedure, or the handling of the pellets, or the site of insertion improved the extrusion rate.

Testosterone pellets are the mainstay of androgen replacement in the Department of Andrology at Concord Hospital. They provide the longest duration of action of any androgen replacement and are convenient, effective and enjoy high continuation rates in this centre.
Nursing Research

Nurses at Concord Hospital contribute to a broad range of research activities which improve our understanding of disease and the quality of care delivered to our patients. The work of three Clinical Nurse Consultants at Concord Hospital is described below.

The “Family Needs” project
Glenda Glynn (Clinical Nurse Consultant, ICU) and Gayle Burr (Professor of Nursing, University of Sydney) have recently conducted a study to establish the needs of family members of patients in the Intensive Care Unit (ICU) at Concord Hospital.

This work was based on the long-held view that there are positive therapeutic effects of family presence and interaction on the critically ill patient. If the needs of family members in coping with the critical illness can be identified and satisfied, they would be better able to contribute to the well being of their relative.

Thirty family members of critically ill patients in Concord Hospital ICU were asked to complete the Critical Care Family Satisfaction Survey, a validated and robust tool for measuring family member satisfaction. The survey covers 5 key areas which provide a framework for needs assessment studies: assurance, information, proximity, support and comfort. Participants were also asked open-ended questions which allowed them to expand on their experience, to identify staff members who were worthy of recognition and to provide information that would help staff take better care of patients and relatives in the ICU.

The researchers also conducted in-depth interviews with five family members in order to further explore views of different aspects of their experience and to establish their overall level of satisfaction.

The researchers found that there was generally a high level of satisfaction from all participants. Both survey and interview groups indicated that they were satisfied with the nature and availability of information regarding their relative’s condition and treatment. However interview respondents added that they had to ask for information or they would not receive it. Respondents were generally satisfied with their proximity to the seriously ill family member, and the comfort of the waiting room. However some criticism of the waiting facilities were made by interview participants (eg need for softer lighting, tea and coffee facilities) who emphasised that family members often spend many hours in the waiting room especially in the first few days when the patient’s condition may be unstable. All participants felt assured that the patient was getting the best possible care, and staff members were seen to be well qualified and professional. There was a general feeling of being well supported by ICU staff, particularly nursing staff.

The results of the study indicate a generally high level of satisfaction from all the interview participants. It is recognised that the family members’ needs for information and effective communication are often problematic, and while this study was not a large one, the researchers noted that these needs could sometimes remained unanswered. Notwithstanding this, the staff of the ICU should be congratulated for generating what appears to be a high level of overall satisfaction for family members, with the care and support provided by the staff in this busy and demanding area.

Management of patients in the Colorectal Surgical Department, using a new bowel management system
Ann Pilley (Clinical Nurse Consultant, Stomal Therapy) and a team from the Colorectal Surgery Department looked at a new system of faecal diversion and containment in immobile patients suffering perineal injuries and incontinence due to excessive diarrhoea.
The bowel management in these patients can involve many techniques including catheters and pouching systems, which are often ineffectual and inappropriately designed. In some circumstances stoma formation (the surgical attachment of one end of the bowel to a small hole in the abdomen) may be necessary. In Australia at present, there is no bowel management technique available. This study was the first Australian assessment of a bowel management catheter system (BMS). The “Zassi Bowel Management System” (ZBMS) multi channel tube was placed by a colorectal registrar or stoma therapist and assessed for ease of use, effectiveness, patient comfort, wound contamination and adverse events.

In the first twenty patients who received the new system, dressing and bed linen changes were reduced to one to two times per day. The average length of rectal intubation was 15 days. No patient complained of pain or discomfort from the tube and assessment by nursing staff found the ZBMS to be satisfactory and commended its future use. In conclusion, the “Zassi Bowel Management tube” was found to be safe and effective, and may help avoid the need for stoma formation in these patients.

Skilled Laboratory Research in the Burns Unit
As we become increasingly successful at saving the lives of those with large burns, our need for a durable permanent skin substitute becomes increasingly acute. It is well documented in the literature that the burn tissue is toxic to the body so if the burnt tissue is removed early, the patient will have a greater chance of survival. Thus the major hurdle for the burned patient and the Burns team is to close the wound after burn excision as soon as possible.

There are several methods to close a burn wound including skin grafts, synthetic skin substitutes, allografts (tissue grafts from another person) and Cultured Epidermal Autografts (CEAs). CEAs are autologous grafts (i.e. using the patient’s own skin or epidermis).

They are cultured in the laboratory from a small skin biopsy (2 square centimetres in size) and then transplanted back to the patient to augment wound closure. CEAs can be harvested as a sheet or spray.

Sue Taggart, Clinical Nurse Consultant (Cell Culturing & ICU Liaison) and colleagues in the Skin Laboratory are undertaking several research projects investigating the use of CEAs. Animal research is being carried out to track the keratinocytes (epidermal cells) from cell spray to the excised burn wound in an animal model. Research is also underway into the evaluation of wound care products that are non-toxic to keratinocytes in cell spray and sheets, once applied to the donor site or graft.

The team has also looked at the requirements of patient information for patients and relatives in the Burns Unit. Twenty patients/relatives were asked what information they would like more of regarding the burn or treatment. This sample of people wanted more information about ‘how deep is my burn’, ‘scarring after burns’ and ‘scar management’. As a result, patient information pamphlets are being developed to reflect the need for more information.

As part of her Honours degree at the University of Western Sydney, Miranda Thomas (RN) and supervisor Sue Taggart audited the clinical progress notes, burns assessment charts, operating notes, wound charts and microbiology reports of 50 burns patients admitted to Concord Hospital in 2005. The researchers looked at the characteristics of donor sites, in patients undergoing skin graft treatment. Specifically, the study sought to compare the different approaches used at Concord Hospital for dressing the donor site, in order to determine predictors of healing, return to functional status and factors which impact on nursing care. The study provided evidence that will support improvements to nursing documentation and wound charts, and will provide valuable information for protocols for burn donor site treatment at Concord Hospital.
The ANZAC Research Institute

The ANZAC Research Institute was established in 2000 on the Concord Hospital campus in conjunction with the University of Sydney. The establishment of the institute ensured dedicated research infrastructure so as to promote basic and applied medical research on the Concord Hospital campus.

The main research theme of the ANZAC Research Institute is ageing, with the long-term goal of prolonging enjoyable, independent living for the ageing population. As the only major independent biomedical research institute with a primary focus on ageing, the ANZAC Research Institute aims to co-ordinate the highest quality innovative research at all levels - from public and population health, to clinical research, molecular physiology (animal models) as well as cell and molecular biology.

Under the overall leadership of its Director, Professor David Handelsman, the major research groups of the ANZAC Research Institute are as follows:

The Andrology group (leader: Professor David Handelsman) is conducting research into male reproductive health, medicine and biology.

The Biogerontology group (leader: Professor David Le Couteur) is studying age-related changes in the liver as they affect drug metabolism and cardiovascular disease.

The Bone Biology group (leader: Professor Markus Seibel) is studying bone disorders, especially osteoporosis and bone cancers.

The Neurobiology group (leader: Professor Garth Nicholson) has its major research focus on the identification of genes that cause neurodegenerative diseases.

The Vascular Biology group (leader: Professor Ben Freedman) is studying the role of oxidative mechanisms and inflammatory factors in cardiac and vascular injury and ischemia, with the aim of improving early detection and developing better treatments for heart disease.

The Cancer Pharmacology group (leader: Professor Stephen Clarke) is studying the ways in which the body handles drugs used for cancer treatment and finding ways to better target cancer treatments.

The ANZAC Summer Student Program

The ANZAC Research Institute piloted the summer scholar research program in the summer of 2003-4. This program was a well-targeted, cost-effective way of achieving a modest increase in the recruitment of postgraduate students to the Concord Hospital precinct. The scholarship involved a tenure of 8 weeks and at the completion of the project each student gave an oral presentation and submitted a written report. This has been a highly successful program for the institute.

Following the first program, two students returned to take part in an honours degree program.

This scheme was presented to the Faculty of Medicine Research Committee as a strategy for increasing postgraduate student numbers. It was recognised that the Faculty of Medicine had an unfilled capacity for PhD students and it was felt that this scheme could assist the Faculty and its affiliated research facilities to establish relationships with students, from both Sydney University and other institutions, which could translate into an interest in postgraduate studies in the future.
In the summer of 2004-5, staff at the ANZAC supervised 8 students on the Summer Scholarship projects. Students involved in the program were from several universities in Sydney and Newcastle as well as from the University of Otago in New Zealand. The summer student program was again a thoroughly rewarding experience for both staff and students.

The success of this program at the ANZAC led to Dr Simon Myers and Professor David Handelsman being awarded the Vice Chancellor’s Award for the student experience (Faculty of Learning and Education, University of Sydney).
The Asbestos Disease Research Centre (ADRC) was established by the NSW Minister for Industrial Relations following lobbying from a consortium of interested unions and victim support groups. The centre was established in order to bridge gaps in the management of asbestos related diseases in NSW. It will focus on the areas of epidemiology, diagnosis, treatment and research.

The ADRC is located at Concord Repatriation General Hospital to develop the most effective and efficient approach to comprehensively address gaps in asbestos related research and treatment. Through its links with the clinical units of Thoracic Medicine and Cancer Medicine at Concord Hospital, the Centre will bring existing organisational arrangements into an integrated network for research, screening, diagnostic and treatment services. The network will also involve Cancer Units at district, base and metropolitan hospitals.

The ADRC will aim to develop novel screening, prevention, treatment and educational strategies for asbestos related diseases, including mesothelioma. Through interaction with NSW Health's Cancer Institute, the ADRC will provide synergies to enhance research, treatment and services. As a centre of excellence, the ADRC with its clinical affiliations at Concord Hospital will lead in the multidisciplinary treatment of mesothelioma and the provision of information and support to other hospitals across the state. This synergy will garner a substantial proportion of all patients suffering asbestos related disease from across NSW for multidisciplinary treatment and will aim to optimise the standards of treatment in a network of hospitals across the state.

The ADRC will have the following key focus areas:

- Improving the screening and monitoring of exposed workers for early diagnosis of mesothelioma and lung cancer.
- Improving research on, and treatment for, mesothelioma.
- Improving education by making available the latest and best research information and counselling services.
Andrology

Researchers in the Department of Andrology at Concord Hospital are undertaking exciting new research which may help prevent prostate disease.

The prostate is the male gland located below the bladder and surrounding the urethra (through which urine flows). As men age, the prostate usually enlarges (benign prostatic hypertrophy or BPH). BPH can result in pain and difficulty passing urine, and sometimes even complete blockage of urine outflow. Such urinary problems are amongst the most common problems associated with male ageing, causing impaired quality of life. These problems require treatment with medication and/or surgery and have a huge impact on the health budget. For example, prostate surgery to rectify prostate overgrowth is the second most frequent reason for major surgery in older Australian men.

Very little is known about the causes of prostate overgrowth and there is no known prevention. The team in the Andrology Department, led by Professor David Handelsman and Dr Anne Conway, in conjunction with an international pharmaceutical company, are conducting a research study looking at a completely new approach to preventing prostate overgrowth. This study requires healthy male volunteers over the age of 50 to apply a daily skin gel for 2 years. This gel will contain either a natural hormone called dihydro testosterone (DHT) or a placebo (no active ingredient). All men will have regular medical examinations including prostate ultrasound every few months.

Men already produce DHT in the prostate gland from the major male hormone testosterone. Previous research studies have suggested that the application of DHT gel can decrease the growth of the prostate in middle-aged men. In order to determine this more clearly, the present study is designed to monitor men over a 2 year period (approximately every 6 months) whilst they apply the gel every day. Regular medical examinations including prostate ultrasound will be undertaken throughout the study. Careful clinical research by experienced medical scientists is required in order to evaluate DHT gel treatment and to provide clues to new forms of prevention for BPH.
The Bone Research Program at the Department of Endocrinology and the ANZAC Research Institute pursues several lines of research relevant to ageing. These include cancer metastasis to bone, glucocorticoid actions in bone-forming cells, male osteoporosis and androgen effects on bone, bone health in children and in the elderly, the genetics of osteoporosis and novel markers of bone turnover.

In 2004, Dr Colin Dunstan, Professor Markus Seibel and the team from the Bone Biology Group were successful in obtaining funding from the NHMRC for research into the mechanisms of breast cancer metastasis to bone. Breast cancer preferentially spreads to bone, where it causes bone destruction that may result in bone pain, fracture and nerve compression. In this project the researchers are looking at why the bone provides such a fertile environment for the growth of breast cancer cells. In addition, they are testing different ways to change the bone environment to make it less supportive of cancer growth.

One strategy that is being used is to target the cells that normally remove old or damaged bone (osteoclasts). These cells are recruited in excessive numbers by the cancer cells to destroy the surrounding bone. In this NHMRC funded study, a natural bone protective agent, osteoprotegerin, is used to stop osteoclasts from forming, thereby inhibiting the growth of breast cancer cells in bone. Further studies will try to identify the signals mediating any such effects. The ultimate aim of this research is to improve treatment of women with breast cancer metastases in their bone, and to develop preventative treatments that could be given to women at high risk of developing bone metastases.

Other exciting research focuses on how certain cells in bone interact with each other. This research demonstrates that there is ‘cross-talk’ between mature bone forming cells (osteoblasts) and their early precursors. This communicating is most likely mediated by a soluble factor and glucocorticoid signalling appears necessary for it to occur. Our studies suggest a novel pathway promoting the formation of osteoblasts, and open a window of opportunity to research the pressing medical problem of “cortisone-induced” bone disease. Wendy Mak, a PhD student in the Bone Research Program, has recently been awarded first prize in the Concord Hospital Research Competition for her work in this area.

From the X-ray of bone containing a breast cancer tumour producing bone destruction (arrow).
The last year has seen a significant increase in the research activities within the Burns Unit at Concord Hospital. The unit has been represented at numerous local and international conferences presenting the results of clinical activities. Eight papers have recently been published in peer reviewed international journals. Numerous major projects are currently underway, several of these in close collaboration with other disciplines within the hospital. Dr Peter Kennedy VMO, former Director of the unit, is now co-ordinating these research activities.

Internationally, new directions in burns research involve combining burns treatment with wound care. This is related to the development of wound care products including bio-engineered materials, and the specialised expertise in wound care available in a multidisciplinary unit. Conditions associated with massive skin loss such as Toxic Epidermal Necrolysis and Purpura Fulminans are now universally referred to regional Burns Units. Several research projects are currently underway documenting advances in the treatment of these conditions within the unit at Concord Hospital.

It is hoped that with the unification of the three tertiary referral units in New South Wales, several multi-centre trials will soon commence, combining both adult and paediatric burn injuries both in clinical studies and in the prevention of burn injuries.

The Skin Culture Laboratory, Concord Hospital Burns Unit

The Skin Culture Laboratory at the Burns Unit, Concord Hospital is part of the NSW State-wide Severe Burns Injury Services. The laboratory provides skin culture services and scientific support to the Burns Units of Concord Hospital, Royal North Shore Hospital and the Children's Hospital at Westmead. In addition to its clinical duties, the laboratory also carries out scientific research, and develops new techniques to improve the clinical outcome of cultured skin cell application in burns wound management.

Effective wound coverage and skin grafting in burns injuries are critical for infection control, stopping body fluid loss and wound healing. However, one of the difficulties in treating patients with large burns is the availability of limited donor sites for skin grafting.

Cultured skin cell autograft is a novel technique by which autologous skin cells (Figure 1) are isolated from a small skin biopsy from the patient, cultured in the laboratory and grafted back to the same patient.

Figure 1
Human skin cell monolayers in cell culture: (A) Dermal fibroblasts; (B) keratinocytes.

Under sterile conditions, the keratinocytes (or skin cells) can be expanded and grown into cultured epidermal autograft (CEA, Figure 2) in either suspension or sheets. The sheets or suspension of cells are about 500 times the...
area of the original biopsy size, after 3 weeks
growth in the laboratory. CEAs provide not only
immediate coverage, but also living cells and
growth factors to facilitate the wound healing
and re-epithelialisation (regrowth of the top
layers of the skin).

Although CEA technology has achieved some
excellent results in burns and donor site
wounds care, its application has some
limitations. The times needed to grow CEA
sheets are sometimes too long, and do not
allow early excision and wound grafting.
Unsatisfactory clinical results have been
observed when epidermal sheets alone are
used for very deep burns involving dermal
damage. Even if the epidermal cells survive,
the quality of reconstructed skin could be poor
and fragile because of the lack of a good
dermal bed to support and facilitate the growth
and differentiation of epidermal cells.

To improve CEA application, efforts are made
in the laboratory to develop dermal and skin
equivalents for deep burn wounds care, and
quick CEA delivery. Using technologies
including tissue culture, cell biology and cellular
and tissue engineering, Dr Zhe Li, the chief
scientist in the Skin Culture Laboratory has
been trying to produce different biological
scaffolds suitable for the growth of skin cells.
To meet the therapeutic regulation standards,
studies are also focused on making the

scaffold animal-product free. All scaffolds will
be biologically compatible, safe and suitable
for skin cells to grow and differentiate into skin-
equivalent tissues. Dermal scaffolds in
combination with CEA technology will be
extremely useful for treating patients with
severe deep burns. The scaffold materials can
be used not only to cover the wound
immediately after early excision, but also to
repair the dermal layers for the subsequent
application of CEAs. Under laboratory
conditions, the scaffolds can be seeded with
autologous dermal fibroblast and vascular
endothelial cells, which will grow and generate
abundant extracellular matrix, growth factors
and blood vessels to form dermis-like
structures. If co-cultured with autologous
keratinocytes, 3D-full thickness skin
equivalents can be developed in culture dishes
with formed epidermis and dermis comparable
to normal skin.

The research and development of tissue-
engineered scaffolds will benefit not only
the burns patient but also the patient with other
skin defects such as chronic, diabetic and
pressure skin ulcers, which are of higher
incidence in the ageing population.
Cancer Research

There has been a significant increase in cancer research activities on the Concord Hospital campus in the last 12 months. This has involved developments in multiple areas including clinical trials of new cancer treatments, nutritional research and psycho-oncology research. In addition, Professor Stephen Clarke and Dr Graham Robertson were awarded a National Health & Medical Research Council (NHMRC) project grant in 2005 to study the factors which impact on the metabolism of drugs in cancer patients.

Support from the NHMRC and the Cancer Institute of NSW has enabled the establishment of a basic research laboratory led by Dr Graham Robertson comprising four Post-Doctoral researchers, three PhD students and two honours students. The focus of the Cancer Pharmacology Laboratory is to explain why different patients experience differences in drug toxicity. The treatment of cancer patients with drugs is difficult due to the fine balance between killing tumour cells and causing toxicity to normal cells. Therefore the huge variability between patients in clearance of anti-cancer agents has a significant impact on the success of chemotherapy. Anti-tumour action may be lost if the drug is cleared too rapidly, while slow drug excretion may lead to extreme toxicity. A better understanding of the source of this variability should lead to improvements in the manner in which chemotherapy is administered and would represent a welcome advance for cancer patients.

The rate of breakdown and elimination of drugs from the body is largely determined by the levels of enzymes called cytochrome P450s (CYPs) in the liver as well as specific drug transporters which move drugs in and out of cells. In humans, CYP3A4 is responsible for the disposal of more than half of all drugs including many important anti-cancer agents. Clinical studies carried out by the Cancer Pharmacology group found that CYP3A4 levels are reduced in some cancer patients, leading to slower clearance of some drugs (such as docetaxel) and ultimately greater toxicity. The source of repressed hepatic CYP3A4 levels appears to be the presence of a marked inflammatory response associated with the growth of the tumour in tissues outside the liver. Therefore a major goal of the researchers is to study the links between inflammatory cytokines released by tumours and down-regulation of drug clearance pathways in the liver. Ultimately the researchers hope to be able to predict which patients will suffer toxicity. It is also hoped that anti-inflammatory treatments can be developed which will normalise drug handling and improve patients’ responses to anti-cancer drugs.
As it is difficult to study these processes in the livers of patients, the Cancer Pharmacology group created a transgenic mouse model of human CYP3A4 regulation. Using these mice, the researchers can carry out experiments to analyse the signalling pathways and molecular mechanisms involved in mediating the inflammatory response to tumours. This knowledge will permit the rational design of anti-inflammatory strategies as well as enabling pre-clinical testing in convenient animal models prior to clinical application. Another source of variability in drug clearance is due to the multiple drugs cancer patients are prescribed as well as the common use of herbal remedies. As many drugs and constituents of herbal therapies can themselves alter the clearance of anti-cancer drugs (by changing CYP3A4 and drug transporter levels) these mice can also be used to screen for such drug interactions.

By identifying the factors which impact on the metabolism and transport of drugs in cancer patients, the research will lead to the safer, more effective use of anti-cancer treatments.

CYP3A4/lacZ transgene expression in tumour-bearing mice

Livers from mice carrying a sarcoma growing in the thigh muscle have reduced levels of expression of the human CYP3A4 transgene. This is shown by lower amounts of darkly stained hepatocytes in tumour-bearing compared with control transgenic mice.
Cardiology and Vascular Biology

The Department of Cardiology has an active research program aimed at increasing our understanding of the degenerative vascular diseases which are so prevalent in the ageing population and are the main cause of death and disability in our community.

The department has also established a Vascular Biology group in the Anzac Research Institute. This is a group of 16 people - scientists, students and clinicians - under the leadership of Professor Ben Freedman. A mix of both basic and clinical science allows research into clinically important disorders of the heart and blood vessels in both experimental models and patients with heart disease.

Investigations with cellular and animal models of stroke

Dr Paul Witting and his team in the Vascular Biology Group at the Anzac Research Institute are carrying out important research into the cellular response to hypoxia and re-oxygenation injury such as occurs during stroke.

Normal neuronal function is crucial to human behaviour. The human brain contains more than 100 billion neurons and requires about 10% of the total cardiac output of oxygenated blood flow. Transient ischemic attack (TIA) or severe stroke brought on through acute oxygen starvation in the brain (eg hypoxia) promotes neuronal cell dysfunction and leads to neurological disability and, in severe cases, death.

Neuroglobin (Ngb) is a novel protein present in neuronal cells. Ngb shows similarities to the oxygen-carrying haem proteins, haemoglobin and myoglobin. The researchers have developed a neuronal cell culture system using a differentiated neuroblastoma cell line (Figure 1).

Exposure of the differentiated neuronal cells to hypoxia and re-oxygenation injury in cell culture provides a model for the response of neuronal cells in the setting of stroke. Using this cell culture model, the researchers are systematically investigating whether Ngb protects neuronal cells exposed to periods of oxygen deprivation or whether Ngb enhances neuronal dysfunction through promoting oxidative stress in brain cells exposed to hypoxic shock. In addition, the group is testing whether a synthetic inhibitor of oxidative stress (Bisphenol) is capable of protecting neuronal cells against hypoxia-reoxygenation injury.
Preliminary data (Figure 2) obtained from supplementing a limited number of rats with the synthetic antioxidant indicate that the drug is readily taken up and is present in both the plasma and the brain of the animals, suggesting that Bisphenol has the potential to inhibit neuronal dysfunction.

Acknowledgement:
This research is being supported by a Grant-in-aid from the CASS Foundation Limited awarded to Dr Paul Witting.

Novel ways to improve outcomes in cardiovascular disease
Dr Harry Lowe and his team in the Vascular Biology Laboratory at the ANZAC Research Institute are examining mechanisms that cause cardiovascular injury at the cell and gene level. The researchers are looking at cardiovascular injury, including restenosis - the vessel re-narrowing that may occur after artery-widening treatment with balloons or stents or in bypass grafts after surgery; and in acute myocardial infarction or heart attack.

By looking at specific genes that are switched on in vascular injury - and switching these genes off using novel catalytic DNA molecules and other agents – the researchers have reduced restenosis and the severity of heart attack in animal models. These studies are performed in collaboration with the Khachigian Laboratory at the Centre for Vascular Research, University of New South Wales.

Dr Lowe and his group are also examining new models of cardiovascular disease and using special techniques of examining human tissue to give more insights into how vascular disease progresses.

Acknowledgement:
Dr Lowe’s work is supported by the National Heart Foundation, National Health and Medical Research Council, Sydney University Research and Development and industry funding. HC Lowe is a Viertel Clinical Fellow for 2005.

Acute Coronary Syndromes including heart attack, unstable angina, and sudden cardiac death
The research teams of both Associate Professor David Brieger and Professor Ben Freedman are using laboratory and clinical methods to investigate the causes, prevention and best treatment of acute coronary syndromes (ACS).

The breakdown of coronary plaques (and consequent coronary thromboses) that underlie...
ACS are thought to be initiated by thinning and breakdown of the wall of plaques by metalloproteinases - enzymes that digest the material in the plaque cap. The researchers have identified a relationship between circulating levels of one of these metalloproteinases, and acutely activated T-lymphocytes – cells that are major players in inflammation. This research has also shown that an unusual type of lymphocyte known to be elevated in ACS was related to chronic rather than acute T-cell activation.

The researchers have examined possible links between inflammation and thrombosis in coronary arteries. C-reactive protein (CRP) is a sensitive marker of inflammation that appears to predict cardiac death and other acute coronary syndromes in both normal populations and those with coronary artery disease. CRP can stimulate blood monocytes to produce tissue factor, the most powerful initiator of thrombosis. The responsiveness of blood monocytes to CRP stimulation is significantly higher in patients with coronary artery disease than in normal controls. CRP therefore appears to be not just a marker of inflammation, but may also play a role in the initiation of adverse events in patients with coronary artery disease by augmenting coronary thrombosis after plaque rupture. Preliminary results also show that SAA (serum Amyloid A) another sensitive marker of inflammation, is a stronger and more rapid stimulator of tissue factor production by blood monocytes than CRP. Once again, monocytes from patients with symptomatic coronary artery disease produce more tissue factor than normal people, suggesting this molecule may play a role in coronary atherosclerosis and its complications, notably ACS. These studies will soon be extended to monocyte-derived macrophages, inflammatory cells which are present in atherosclerotic coronary artery vessel walls, and appear to be important mediators of ACS.

To better understand what factors are important in determining outcome of patients who present to hospital with an ACS, the Cardiology Department is participating in a large multicentre multinational study (the GRACE study), and Concord Hospital is the coordinating centre for Australia. These studies have identified a number of novel factors including a new risk score to determine who is most at risk for major events in the first year after an ACS.

After ACS, cardiac rehabilitation has been shown to be beneficial, but it is difficult to provide this to all patients, and uptake of the service is very limited. In a novel approach to cardiac rehabilitation, Julie Hila, a physiotherapist, is trialing a modular approach based on empowering patients to modify their own risk factors. In the preliminary part of the study, she has found that the risk factor profile of those who are not attending cardiac rehabilitation is significantly worse than those who do attend, and that overall knowledge of their own risk factors is poor in patients between 3-6 months after an ACS.

In heart attack, current therapy is centred on removing the underlying clot with either clot dissolving drugs, or balloon angioplasty. Researchers in the Cardiology Department are investigating novel methods to dissolve blood clots in a mouse model deficient in plasminogen (the precursor of the natural protein which can dissolve clots). They have found increased clot dissolving activity in the neutrophils of these mice, and the compounds responsible for this activity are being identified and characterised. These findings may lead to new and more effective clot dissolving therapy as well as providing insights into the natural defense after blood clots have formed in heart attacks.

Acknowledgements:
This work is supported by a National Heart Foundation grant-in-aid, a Sydney University Research and Development grant, a Pfizer Cardiovascular Lipid grant, and Pharmaceutical Industry funding.

Imaging of heart and blood vessels
A group led by Associate Professor Len Kritharides is studying computer tomography (CT) and echocardiography imaging of the heart and blood vessels, with close collaborations between Dr Lloyd Ridley in Radiology, Dr Van der Wall in Nuclear Medicine
and Dr Ilona Cunningham in Haematology. Studies performed by Dr George Lau (see page 8) are investigating CT angiography and its potential to study coronary artery bypass graft disease. Dr Lau has identified that vein graft thickening occurs very early after cardiac surgery and is related to the presence of preoperative diabetes. He has also shown that vein grafts shrink in the first year after surgery, and that elevation of a component of blood fats, namely triglycerides, are related to early closure of arterial grafts.

Dr Tommy Chung is investigating reversible dysfunction of the heart pumping action caused by the commonly used chemotherapy treatments for certain blood cancers. Results to date suggest a surprisingly frequent incidence of silent cardiac injury. He is also assessing the impact of pulmonary emboli (blood clots in the lungs) on the pumping action of the right ventricle by echocardiography. Collaborations with Dr Emmett in the Department of Nuclear Medicine have shed light on the mechanism of an important finding in cardiac nuclear stress testing (transient ischaemic dilatation), and others with Dr Yiannikas of Cardiology and Dr Allman of Nuclear Medicine indicated that inflammation may occur in some coronary arteries after stenting using certain drug-eluting stents.

The Ageing Liver and Transport of Blood Fats
In this study led jointly by Associate Professor Len Kritharides and Professor David Le Couteur, the fate of apoE (a protein that can transport cholesterol and other blood fats) in liver cells is being investigated by Ms Sabaretnam, to determine the effects of ageing and oxidative stress. Initial results of these studies indicate that there is altered trafficking of apoE with both ageing and oxidative stress, and that this may contribute to altered cellular apoE distribution found in vivo.

Clinical studies into Chronic Heart Failure: The CIBIS III Study and the UNIVERSE study
Despite the development of new drugs, Chronic Heart Failure (CHF) remains a major clinical and public health problem and accounts for a significant proportion of health costs. The introduction of ACE (angiotensin converting enzyme) inhibitors and ß-blockers in the treatment of CHF in the last two decades have been major milestones. ACE inhibitors in combination with ß-blockers have been proven to slow the progression of CHF, improve symptoms in the long term, reduce the number of hospitalisations, and increase survival. The question of whether the treatment of heart failure should always be started with an ACE inhibitor, followed by the addition of a ß-blocker or whether an ACE inhibitor is required at all in patients treated with ß-blocker has still to be answered.

The CIBIS III study is an international trial involving 1,000 patients with chronic heart failure. It compares the efficacy and safety of initial treatment with bisoprolol (a ß-blocker) versus enalapril (an ACE inhibitor) as monotherapy, followed by a combination of the two drugs. The trial is being conducted at Concord Hospital Cardiology Department under the direction of Professor Andrew Sindone.

Professor Sindone and his team are also involved in a large multi-centre study (the UNIVERSE study) looking at cholesterol-lowering drugs and CHF.

It is known that lowering cholesterol with HMG CoA reductase inhibitors (statins) results in significant reductions in mortality and cardiovascular events, in comparison to placebo, in patients with normal and high levels of plasma cholesterol and proven coronary artery disease. However, the UNIVERSE study is the first prospective study to elucidate the benefits of statins on patients with established CHF. This study is to determine whether Rosuvastatin (a statin) is superior to placebo in heart function, cardiac inflammation, lipid levels and hospitalisations. Validation of this hypothesis in the trial would be an important advance in the management of CHF.
The Centre for Education and Research on Ageing (CERA)

CERA is a multi-disciplinary centre on the Concord Hospital campus, which is a joint facility of the Aged and Extended Care Department of Concord Hospital and the Department of Medicine, University of Sydney.

One of the functions of CERA is to conduct an integrated, multi-disciplinary programme of epidemiological, clinical, biological and health service research on ageing. Research at CERA is concerned with the ageing process, and the disorders and diseases that are most likely to cause disability and reduced quality of life in old age. Chief amongst these are dementia, falls, delirium, immobility and instability, loss of independence and the need for institutional care.

Basic science research at CERA is undertaken in the centre’s two basic research laboratories, the Biogerontology Research Laboratory in the ANZAC Research Institute and the Neuropathology Research Laboratory at Concord Hospital. The work of the Biogerontology Laboratory will be facilitated over the next three years by two National Health & Medical Research Council (NHMRC) grants awarded to Professor David LeCouteur to study the mechanisms of ageing changes in the liver.

The Concord Health and Ageing in Men Project (CHAMP)

In 2004, Professor Bob Cumming and a group of his colleagues from Concord Hospital and the ANZAC Institute were awarded a $1.7 million project grant by the NHMRC to carry out a 5-year study into the health of older men in the local community.

CHAMP is a multidisciplinary, epidemiological study designed to provide a wide range of new information about the health of older men. Despite the fact that men who reach the age of 65 still have much lower life expectancy than women of that age, very little research has been done on the health of older men. CHAMP has been designed to fill this gap and is arguably the world’s most comprehensive study of the health of older men. Primary hypotheses concern the role of reproductive hormones in the aetiology of osteoporosis, muscle weakness, urinary symptoms and dementia.

Over 2000 men aged 70 years and over who live in the community near Concord Hospital will be invited to participate in CHAMP. Prior to attending the study centre at Concord Hospital, participants will complete a series of questionnaires. They then spend about 3 hours at the study centre, where a series of tests are done, including blood tests for hormones. Blood is stored for DNA testing, in order to study aspects of the molecular biology of ageing. Most of the baseline interviews and examinations are repeated after 2 years.

The CHAMP study, will give valuable information about a range of specific issues of men’s health:

Bone fragility and fractures - Fractures are common in older men. Almost 30% of 60 year old men will have a fracture of some type during the remainder of their lifetime. CHAMP is one of the first studies in the world to investigate risk factors for fractures in men. CHAMP will be far larger than any previous study of osteoporotic fractures in men in Australia, second in size only to the “Mr Os” Study in the United States. All men in CHAMP have their bone density assessed using dual energy x-ray densitometry (DEXA), as well as biological markers of bone turnover and physiological measures of neuromuscular function.

Muscle weakness and muscle loss - There is some evidence that men lose muscle at a faster rate than women as they grow older. CHAMP uses sophisticated techniques
The Centre for Education and Research on Ageing (CERA)

including DEXA) and a longitudinal design to assess muscle mass and function in older men.

Cognitive impairment and dementia - Dementia is probably the most disabling condition of old age, yet little research has been done on the special features of dementia in men. CHAMP will be the world’s largest study of dementia in men. CHAMP has a particular focus on testosterone and the aetiology of Alzheimer’s disease. All men in CHAMP complete a 30-minute neuropsychological screen and those with low scores return for a more detailed clinical and neuropsychological assessment.

Lower urinary tract symptoms and incontinence - Many older men develop lower urinary tract symptoms such as nocturia, weak stream and dribbling. Furthermore, at least 15% of men over 65 years have some degree of urinary incontinence. It is generally believed that urinary problems in older men are due to their enlarging prostates. However, the causes are likely to be much more complex. Urinary function is assessed in CHAMP using a urinary flow meter and bladder ultrasound to measure post-void residual urine. Blood is being collected for Prostate Specific Antigen (PSA) measurement.

Navigating the change process; the experiences of, and ways forward for, facility managers in residential aged care

Chris Shanley (Assistant Director, Education and Information Services, CERA) is undertaking research into the effects of changes in the residential aged care sector on aged care facility managers.

The residential aged care sector in Australia has been undergoing multiple changes over the past decade, caused by factors such as new regulatory systems and new models of care. Managers of residential aged care homes, such as nursing homes and hostels, are at the forefront of managing these changes.

The aims of this study are to build up an understanding of how facility managers see their role and how they approach the management of change. The study also aims to develop a comprehensive model of change management that is relevant to the residential aged care sector.

Early findings from interviews with aged care facility managers indicate that insufficient attention is being paid to the management of change, and that facility managers are not given explicit preparation and support in this aspect of their role. This can lead to stress on the managers and difficulty in successfully implementing the change programmes. The study expects to provide a number of recommendations about how facility managers can be better supported in this important aspect of their position.

“White matter hyperintensities” in the ageing brain

Magnetic resonance imaging (MRI) often reveals areas of high signal intensity in the cerebral white matter of elderly people. These lesions are known as “white matter hyperintensities” (WMHs) and have been associated with numerous disorders including cerebrovascular disease, dementia and gait disturbances. Despite a variety of investigations into this phenomenon, the origin and significance of WMHs remains unknown.
The Centre for Education and Research on Ageing (CERA)

The ability to correlate WMHs with the appearance of the brain under the microscope, is fundamental to determining the cause of these lesions. However, attempts to do so are inherently flawed as a result of tissue changes occurring between the time of the in vivo MRI scan and death. Postmortem MRI would therefore be a useful tool, but some studies have reported that postmortem MRI of formalin-fixed tissues detects WMHs with less sensitivity compared with in vivo MRI.

PhD candidate Vanessa Young and Associate Professor Jillian Kril from CERA have developed a protocol to obtain high-resolution MR images of formalin-fixed human brain that are comparable with the MRI images obtained in vivo.

Using brains obtained from participants in a brain donor programme, which were fixed in 15% formalin, MRIs were performed on a 3.0-T scanner (Philips Medical Systems). Scan sequences were modified until WMHs were visible.

This study has demonstrated that high quality postmortem MR imaging of formalin-fixed human brain is possible and that WMHs are detected with a sensitivity comparable with that of in vivo scans. Correlative neuropathological studies are now underway to determine the composition of these lesions, which in turn could lead to the elucidation of their cause.

The Concord Acute Hip Fracture Database

Hip fractures are the leading cause of hospitalisation for injuries in older persons. The risk of hip fracture increases dramatically with age. Four per hundred women aged 85 years and older will experience a neck of femur fracture each year in NSW.

Concord Hospital admits approximately 130 proximal hip fracture patients per year, with an average age of 80 years. In 1993, a team approach was initiated for the management of proximal femur fractures. This Orthogeriatric service involves the cooperation of all the disciplines involved in the care of these patients- surgery (Orthopaedic surgery), medicine (Geriatric Medicine), nursing, physiotherapy, occupational therapy and social work. The service involves shared management of patients during the pre- and postoperative periods, as well as during the rehabilitation phase of care.

In 2004, Dr Laura Ahmad from CERA established a programme of standardised data collection from patients who have suffered a hip fracture. This database includes detailed information about patients’ functional status, comorbid conditions, results of routine laboratory investigations, operative management, hospital course, discharge functional status, and discharge destination. Patients are approached for permission to be included in the research during their initial assessment. This database is being used to describe the population of hip fracture patients at Concord Hospital in terms of demographic information and short term outcomes, and to compare with published guidelines for care. In the future it could be used to look at longer-

Figure A
In vivo MRI showing WMHs in both the frontal and occipital lobes.

Figure B
Postmortem MRI of the same patient 5 years later. WMHs can be seen in the frontal and occipital lobes, although they are now more severe in the frontal lobes.
term mortality and functional outcomes, and could be used in other hospitals to allow comparisons between centres, as well as pooling of data. This database may also serve as the basis for interventional trials in the future as new management techniques for hip fractures become available.

The Ageing Liver
The Biogerontology Laboratory was established within the ANZAC Research Institute at Concord Hospital in January 2001 and is the biological research arm of CERA. The primary role of the research group is to study the biology of ageing. Due to its major role in detoxification and lipid (fat) metabolism, the liver is of particular interest.

It is well recognised that drug metabolism in older persons can be impaired, a situation that can lead to over medication with the possibility of adverse events such as falls and fractures. Similarly, it is recognised that the time to clear dietary lipid products (chylomicron remnants) from the blood after a meal is prolonged in older persons compared to those of younger age, a situation that can increase the risk of cardiovascular disease. By studying the differences between young and old livers, the Biogerontology Group has identified structural changes in the liver that explain these age-related phenomena.

Researchers within the Biogerontology Laboratory have been studying the small holes called fenestrations in the endothelial cells lining the terminal capillaries (or sinusoids) of the liver. These fenestrations are arranged in plates that act as molecular sieves, and control the flow of substances into the liver. It has been found that with increasing age there is a reduction in the diameter and number of fenestrations in addition to thickening of the sinusoidal endothelium and the development of a basement membrane that acts as a physical barrier to further impede the transport of substances into the liver. Together these structural changes help explain why drug metabolism is impaired in older people and why it takes longer to clear dietary lipid from the bloodstream.

The work undertaken within the Biogerontology Laboratory continues to improve our understanding of how drug and lipid metabolism by the liver changes with advancing age and how these changes may adversely impact the health of older persons.
Research within the Department of Gastroenterology is diverse, spanning many fields of clinical Gastroenterology.

Amongst the main areas of interest are research into peptic ulcer disease, gastro-oesophageal reflux disease, inflammatory bowel disease and colorectal cancer. The Gastroenterology Department has also carried out research into the prevalence, antibiotic resistance and treatment of *Helicobacter pylori*.

The Department has an interest in endoscopic research, including studies on the utility and application of endoscopic ultrasound and other advanced endoscopic techniques.

Hepatological research includes the development within the Department of a novel, non-invasive quantitative test of liver function (described in more detail below), as well as therapeutic studies of antiviral therapy for hepatitis B and hepatitis C.

Ongoing collaborative studies are in progress with research groups at the University of Sydney, University of NSW and Westmead Hospital as well as some evolving collaborative links with centres in South East Asia.

The **¹³C-Caffeine Breath Test as a Non-invasive, Quantitative Test of Liver Function**

Assessing the degree of liver damage associated with a particular liver disease often relies on performance of a liver biopsy. However, this procedure entails certain risks such as bleeding and pain, and generally requires hospitalisation which is costly and inconvenient. Furthermore, the samples of liver tissue obtained from the biopsy may be too small to make an accurate diagnosis. Thus, much interest has focused on developing non-invasive ways of estimating liver damage as potentially safer alternatives to liver biopsy.

One approach is to measure how well the liver metabolises or breaks down chemicals such as those found in foods and drugs. In recent years, researchers in the Department of Gastroenterology have been developing a test which measures the capacity of the liver to break down caffeine, a process almost exclusively confined to the liver. The test, which can be conducted in any outpatient setting, involves patients fasting overnight and then drinking a solution of caffeine (equivalent to two cups of coffee) which has a special carbon tag. Patients simply blow into a test tube before and one hour after drinking the caffeine.

In a healthy liver, the caffeine would be rapidly broken down. The carbon tag would be released into the body, incorporated into carbon dioxide, then exhaled and measured. The more damaged the liver, the less of the carbon tag would be found in a patient’s breath.

Dr Gordon Park, as part of his PhD candidature in the Department of Gastroenterology, has carried out studies validating the caffeine breath test (CBT) as a safe, reliable and accurate method of estimating liver function in a variety of liver disorders. In patients with chronic hepatitis B infection, the CBT was able to distinguish patients who had developed advanced fibrosis or scarring of the liver from those with little liver damage. The breath test was more sensitive than conventional blood tests in detecting the scarring. In addition, by applying the test serially in the one patient, the CBT was able to monitor a patient’s response to drug therapy against the hepatitis B virus. Thus, it could be used to track the progression of liver disease and response to treatment within individuals over time. Similar results have been obtained using the CBT in patients with chronic hepatitis C infection, alcoholic liver disease and cirrhosis (severe scarring). Studies are also underway in patients with fatty liver disease and haemochromatosis (excess iron in the liver). The effects of ageing on normal liver function are also being explored.
Although the CBT is still undergoing trials at Concord Hospital, it is hoped that it will soon be available to the wider public as a simple and non-invasive way of estimating liver function and damage associated with a wide spectrum of liver diseases.

**Funding:**
Dr Gordon Park was the recipient of a Postgraduate Medical Scholarship from the National Health and Medical Research Council (NHMRC).

**Pharmaceutical Clinical trials**
Members of the Gastroenterology Department are actively involved in a number of multi-centre clinical trials investigating treatments for a range of debilitating conditions.

Associate Professor Peter Katelaris and his team are undertaking clinical trials looking for improved treatments for *Crohn’s Disease* (a chronic inflammatory bowel disease) and *Irritable Bowel Syndrome* (a common disorder of the gastrointestinal tract characterised by abdominal pain and discomfort). A study investigating a new treatment for *Clostridium difficile* - associated diarrhoea (which is commonly acquired in hospital) is also underway in the department.

Dr Alice Lee and Associate Professor Meng Ngu are involved in multi-centre trials looking at effective treatments for chronic hepatitis B and hepatitis C. Hepatitis C is the most frequently notified communicable disease in Australia with an estimated 225,000 Australians having been exposed to the virus. Dr Alice Lee is coordinating the GET-C (Genotype 3 Extended treatment for hepatitis C) study at Concord Hospital. This study is investigating the tailoring of anti-viral therapy to the individual characteristics of patients. This study will look at patients infected with a particular strain (the *genotype 3* strain) of the hepatitis virus, and will investigate whether improved outcomes can be gained by individualising dosage and duration of anti-viral therapy according to genotype, viral load and weight of the patient.
Immunology

Dr Sean Riminton (staff specialist) and Philippa Kirkpatrick (project co-ordinator) have designed and implemented the Australia and New Zealand Primary Immune Deficiency (PID) register at Concord Hospital. The database is hosted and maintained by the George Institute for International Health.

Primary immune deficiency diseases are a group of potentially serious disorders in which inherited defects in the immune system lead to increased infections. Symptoms and signs of illness may not develop until adult life, commonly appearing as recurrent bacterial infections in the chest and nasal airways.

Most primary immune deficiency diseases are rare, but collectively they represent a very important and diverse group of diseases, requiring specialised care and treatment.

The Australasian Society of Clinical Immunology and Allergy (ASCIA) has established the PID register in order to gather comprehensive information about how these illnesses affect people living in Australia and New Zealand. The register is an online database of patients with PID disease and its objective is: “To collect and analyse data on all patients with PID in Australasia to facilitate diagnosis, treatment, research, education and quality assurance for patients with PID and their health care providers, and to guide the use of immunoglobulin replacement resources”.

Patient consent is required before entering details into the register. Patient names are not identified on the register and access to the register is restricted. However, there is a public website which has information about the register and PID diseases (www.immunodeficiency.org.au).

By the end of July 2005, the PID register held data on 1,057 patients in 105 centres. The current Australian reporting rate for PID is approximately 5 per 100,000 people.

Fifty-four separate disorders have been reported, affecting individuals with an age range from less than one year to 94 years (mean age 28 years). 77% of reports involved defects of antibody production with common variable immunodeficiency (CVID) being the single most common diagnosis. The second most common disorder was Immunoglobulin G subclass deficiency, accounting for approximately 16% of patients.

The register has revealed that potentially preventable complications of PID (such as bronchiectasis and sinopulmonary infections) are common and that the use of immunoglobulin replacement therapy appears to be increasing. Data collection is active and ongoing.

Acknowledgement:
The PID Register is supported by an ASCIA grant and unrestricted grants from CSL Bioplasma Ltd and Octapharma Ltd.
Research in the Department of Infectious Diseases and Microbiology covers a range of areas. These include investigations into bacterial resistance to drug treatment; population-based studies of infections in patients presenting to Australian hospitals; and the evaluation of a point of care test to diagnose pneumococcal pneumonia in the Emergency Department.

Resistance in the Bacteroides fragilis group: New superbugs in waiting?
Anaerobic bacteria have been shown to represent a large proportion of the microbes present in infections. A study in 2004 by Dr Steve Siarakis and Helen Boyd from the Department of Microbiology demonstrated increasing resistance to antibiotics in a group of anaerobic bacteria, Bacteroides fragilis, in hospital and community patients. Increasing resistance has significant implications for the treatment of anaerobic infections particularly in elderly hospitalised patients with nosocomial infections (infections acquired while in hospital, such as aspiration pneumonia, diabetic foot ulcers and abdominal infections).

The researchers further found that individual members of the Bacteroides fragilis group showed varying levels of resistance to the different antibiotics tested. The species analysis highlighted the importance of accurate species identification in the determination of clinical therapies.

The increased levels of resistance demonstrated in this study suggest that the Bacteroides fragilis group will require constant monitoring and will likely be the next group of superbugs reported.

Changing epidemiology of multiresistant Acinetobacter baumannii in intensive care burns unit patients
Dr Tom Gottlieb, Dr Ross Bradbury and Dr Elaine Cheong carried out a study to document the changing epidemiology of Acinetobacter baumannii in Concord Hospital patients over the period 2000 to 2004. This review allowed the researchers to specifically assess the impact of an external source of multi-drug resistant Acinetobacter baumannii (MRAB) following the Bali bombing in October 2002.

Acinetobacter infections are common in burns patients and in ventilated patients in the Intensive Care Unit (ICU). An original strain ("phenotype A") of MRAB appeared in Concord Hospital patients in July 2000 and was the dominant MRAB phenotype until the Bali bombing in October 2002. At this time eight victims were admitted to the ICU. Seven of these patients were colonised with MRAB, with 12 different susceptibility phenotypes demonstratable (see Figure 1). All differed to MRAB clone A. Some of these strain types have now supplanted the original clone A, as dominant MRAB epidemic strains.

Increasing multidrug resistance is an ongoing problem in Intensive Care and Burns Unit patients.
Infectious Diseases and Microbiology

A rapid test for the detection of *Streptococcus pneumoniae* antigen in urine

A study was undertaken in the Emergency Department of Concord Hospital in 2004 to evaluate the “Urinary Antigen” test for the diagnosis of pneumococcal pneumonia.

*Streptococcus pneumoniae* is the most common cause of pneumonia in the elderly. Confirming the diagnosis of pneumococcal pneumonia traditionally relies on isolation of the organism in blood or sputum culture, which can take from 24 to 48 hours. However, a simple urinary test carried out in the Emergency Department was shown to give a rapid and reliable bedside diagnosis for *Streptococcus pneumoniae* within hours, rather than days. In addition, routine use of the tests enhances detection of the organism when compared to standard microbiological culture techniques.

The advantages of having a test which can be reliably performed and interpreted by clinical staff at the point of care, means that appropriate and rapid antibiotic treatment may be initiated. This test may reduce the use of broad-spectrum antibiotics (and the possible emergence of antibiotic resistance) in patients with community-acquired pneumonia.

The Australian Scedosporium Study and the Australian Candidaemia Study

The Microbiology Department has been involved in two prospective multicentre population-based studies documenting infections in patients presenting to Australian hospitals, including Concord Hospital. The Australian Scedosporium study is a national study examining the epidemiology and clinical features associated with *Scedosporium* spp, a fungus that is usually found in soil and may cause infection via inhalation of aerosolised spores or hyphae. Similarly, the Australian Candidaemia Study is a study of the epidemiology, clinical presentation and management of candidaemia in Australia over a 3-year period. The fungus *Candida* is a major human pathogen and a leading cause of bloodstream infections in patients in hospital.

The Department is also a member of AGAR (the Australian Group on Antimicrobial Resistance), a group of laboratories participating in federally funded active surveillance studies of antimicrobial resistance in Australia (http://antimicrobial-resistance.com/).
Researchers from the Intensive Care Unit and the Respiratory Unit at Concord Hospital have collaborated on an audit of admissions to the hospital's Intensive Care Unit for patients with severe community-acquired pneumonia (CAP). Other ICU research has focused on the trends in ICU admissions for elderly patients in Australia.

Severe Community-Acquired Pneumonia Requiring Intensive Care Unit Admission
Dr Elizabeth Fugaccia (ICU), Dr Elizabeth Veitch (Respiratory Medicine) and Dr Graeme Thompson (Respiratory Medicine) carried out an audit of patients admitted to the Intensive Care Unit with severe community-acquired pneumonia during the period July 2000-June 2003.

Amongst the 50 patients admitted during this period, 68% were males and the mean age of patients was 67.6 years (range 24-93 years). A history of current or prior smoking was common (64% of patients). Significant comorbidities existed in 49 of the 50 patients, including CCF (congestive cardiac failure), COPD (chronic obstructive pulmonary disease), chronic liver disease, chronic renal failure, and diabetes. A causative organism was identified in 48% of patients (see Figure 1). It was found that 30% of patients had received antibiotics prior to admission, but this did not influence the detection of a causative organism.

Patients hospitalised with severe CAP during the period of study received invasive ventilation (92% of patients), and tracheostomy was required in 4% of patients. Severe community-acquired pneumonia remains a major problem, with a high mortality when ICU admission is required. 48% of patients admitted with severe community-acquired pneumonia died. Mortality was not associated with age or the presence of a known pathogen. However, APACHE II and SAPS II scores (methods for assessing the severity of illness in acutely ill patients in intensive care units) were highly predictive of outcome.

The team plans an ongoing audit of the management of severe community-acquired pneumonia at Concord Hospital. Given that a greater range of treatment options has recently become available (including newer antibiotics targeting pathogens causing pneumonia), it is hoped that the research will give information, which could guide future patient management.

The initial results of the CAP audit were presented in poster format at the Asia-Pacific Society of Respirology Meeting, held in Hong Kong in December 2004.

Figure 1
Pathogens isolated in cases of severe Community-Acquired Pneumonia (CAP) in patients admitted to Concord Hospital Intensive Care Unit, July 2000 - June 2003.
Trends in intensive care admissions of elderly patients in Australia

In Australia, as well as other developed countries, life expectancy is increasing. Combined with the falling birth rate, and better general health and living standards, this has resulted in an increasing proportion of the population living to a healthy old age. The increasing number of elderly persons (those aged 80 years or over) in the Australian population suggests that an increase in this patient population as a proportion of Intensive Care admissions will occur.

Dr Elizabeth Fugaccia from the Intensive Care Unit (ICU) at Concord Hospital conducted an audit of ICU admissions for the years 1996-2003, in collaboration with colleagues from Fremantle Hospital, Western Australia and Westmead Hospital, Sydney.

All admissions to the three tertiary ICUs between 1 January 1996 and 31 December 2003 were reviewed. Age, sex, admission dates, discharge dates and outcomes were recorded. This data was compared to data collected for the ANZICS (Australian and New Zealand Intensive Care Society) Adult Patient Database for the same period.

The study found that the numbers of admissions of people aged 80 years and over increased in each of the three ICUs. The relative increase in the proportion of ICU admissions aged 80 years and over at each participating unit varied (Fremantle 17.9%; Concord 54.7.% and Westmead 72.2 %). This compared with an overall increase in similar admissions (reported to the ANZICS Adult Patient Database from Australian Intensive Care Units) of 30.6 %. The peak age of admissions at all sites was also shown to increase (Figure 2).

Hospital outcomes for patients admitted to Intensive Care remained similar between 1996 and 2003: 55.5% of patients were discharged home; 26.1% died in hospital; 8% were transferred to a rehabilitation facility and 10.4% were transferred to another hospital or ICU.

The study concluded that an increasing proportion of ICU admissions are occurring in patients aged 80 years and over, in keeping with the increasing number of elderly persons in the general community. This is a trend throughout Australia in Intensive Care, and is expected to accelerate in the future. More work is urgently required to examine the influence of Intensive Care admissions on the subsequent quality of life and functional status of elderly patients. This will enhance the dissemination of factual information to the general community with the benefit of promoting informed medical decision-making by, or on behalf of the elderly.
The prevalence of obesity in the Australian adult population has reached epidemic proportions. It is now approximately 20% and rapidly increasing. As a result, the incidence of diabetes and prediabetes has dramatically increased.

In order to address this major health issue, the Departments of Endocrinology & Metabolism at Concord Hospital and Royal Prince Alfred Hospital, Sydney South West Area Health (Departments of Nutrition & Dietetics, Physiotherapy & Psychology), the NSW Institute of Sports Medicine, Bayer Australia, Novartis Consumer Health and Servier Laboratories have joined together to introduce a new and unique clinic to best treat this patient population.

The clinic was launched on the 9th September 2003 with the state and local members of parliament, community organisation representatives and members of the public. Since then, patients have been attending the clinic to be assessed and managed by a large multidisciplinary team.

The primary focus of the clinic is to help patients achieve a healthier weight and improve their fitness, which will then lead to improvements in blood glucose, blood pressure and cholesterol levels. As part of the program patients attend supervised exercise classes at the NSW Institute of Sports Medicine (opposite Concord Hospital).

The results of a feasibility study examining the initial patients who attended the program for at least six months were analyzed by NHMRC Scholar, Dr Abdullah Omari. Dr Omari subsequently presented these results at the European Congress of Obesity Annual Scientific meeting in Athens. It was found that patients were able to achieve six percent weight loss, a reduction in their waist circumference by nine centimetres and better control of their blood sugar levels. In addition to this, patients achieved improvements in their blood pressures and blood cholesterol levels, with 63% of patients having a reduction in their medications. The reductions in medications lead to a $560 cost saving for patients in the first six months.

In 2006 a large randomised controlled trial examining this novel clinic is planned. It is hoped that this study will determine which model of ambulatory care is best for treating adults with the metabolic syndrome.

Some of the MRC team are pictured above. (Left to right) Angie Nikas (exercise physiologist), Dr Abdullah Omari (NHMRC Scholar in the metabolic syndrome), Dr Mridula Lewis (advanced trainee in Endocrinology), Meredith Kearney (psychologist), Dr Nic Kormas (Endocrinologist), Karen Evans (exercise trainer) and Rosemary King (dietician).
Neurology

The principal areas of research for the Concord Hospital Neurology Department are in the management and secondary prevention of stroke, the treatment of Parkinson's Disease and the investigation of adult muscle disorders.

Associate Professor Alastair Corbett, director of the Stroke Unit, is the local investigator on a multicentre trial for stroke prevention called the "On Target" trial. This is a trial of 2 antihypertensive agents – ramipril (an Angiotensin converting enzyme blocker) and telmisartan (an Angiotensin 2 receptor blocker), used either individually or in combination to prevent recurrent strokes in patients with cerebrovascular disease.

The "Interact" trial is a study investigating blood pressure lowering in patients with acute intracerebral bleeds (bleeding within the brain). Current practice is for acute treatment of these patients without aggressive lowering of blood pressure. The Interact study will randomise cerebral haemorrhage patients for either standard care or more vigorous treatment of hypertension. Evaluations will include measurement of cerebral blood perfusion.

Current studies into neuromuscular disease include a study of the effectiveness of modafinil, a novel non-amphetamine alerting agent, in controlling excessive day time sleepiness and apathy in patients with myotonic dystrophy, a disorder causing lethargy and sleepiness. Patients are being assessed both on and off medication using multiple sleep latency testing, neuropsychological evaluations and instruments to measure sleepiness and apathy. Modafinil, which has recently been approved for use in treating narcolepsy, appears to be of significant benefit to patients with myotonic dystrophy.

Further planned studies include an assessment of male health, endocrine disorders and heart function in patients with myotonic dystrophy.

Dr Michael Hayes of the Neurology Department is carrying out clinical research into new treatments for Parkinson's Disease (PD). The Department continues with two follow-up open-label stages of large international multi-centre studies sponsored by Schwarz Biosciences. Both studies use a novel dopamine agonist, rotigotine, in the form of a skin patch. The first study involves a group of patients with relatively mild PD, and a second study is examining the role of rotigotine in those with relatively advanced PD. Results from the earlier randomised, double-blind, placebo-controlled phases of these studies should be available in the near future.

The results of another international multi-centre study with which the department was associated, were published in the last year. This study looked at the use of an investigational drug, sumanriole, in the treatment of PD. Unfortunately, sumanriole did not appear to offer any advantages over ropinirole, the comparator drug, and the sponsor decided to withdraw any further promotion of sumanriole. This decision remains an issue in Australia where there is still no PBS subsidised access to non-ergoline dopamine agonists.

Currently, researchers in the Neurology Department are involved in the QUEST-AP study (Quality of life Evaluation of Stalevo-Asia Pacific), a double-blind, placebo-controlled study examining the role of the drug entacapone in possibly enhancing quality of life in patients with PD. This study is unusual in that Novartis Pharmaceuticals has sponsored a regional study involving Australia, Philippines, Taiwan, Thailand and Malaysia.
The large cohort of patients within the PD clinic has allowed collaboration with researchers from other institutions, particularly with Professor Glenda Halliday at the Prince of Wales Medical Research Institute. A paper on genetic anticipation in familial PD has recently been submitted to a peer-reviewed journal.

In other research, Dr Michael Hayes has been involved in collaborative work with Dr Matthew Kiernan and Dr Arun Krishnan at the Prince of Wales Hospital on electrophysiological characteristics of hemi-facial spasm. The Neurology Department also contributed to a retrospective study of multiple sclerosis (MS) therapy sponsored by Biogen Australia.
Molecular Medicine and Northcott Neuroscience Laboratory

Researchers from the Department of Molecular Medicine and the Northcott Neuroscience Laboratory at the ANZAC Research Institute are undertaking studies that are providing insight into the mechanisms causing nerve degeneration, a process that is highly relevant to the ageing process.

The group, headed by Professor Garth Nicholson, has continued to make important contributions to finding gene mutations causing degeneration of peripheral nerves and motor neurons. The laboratory runs two research programs concurrently: the gene mapping and discovery program and the cell biology program under the direction of Dr Marina Kennerson and Dr Simon Myers, respectively.

Inherited Peripheral Neuropathies
Charcot-Marie-Tooth (CMT) neuropathy is the most common group of human hereditary disorders. The syndrome is a disorder of peripheral nerve affecting both motor and sensory neurons. In collaboration with their American and European colleagues, the researchers have identified mutations in the dynamin 2 (Dyn2) gene causing dominant intermediate CMT (DI-CMTB). Dynamin 2 is a large enzyme involved with receptor mediated endocytosis (RME). The researchers have shown that patient lymphoblast cells stained for dynamin 2 displayed altered intracellular localisation of the protein compared to controls (Figure 1).

Figure 1
Control and DI-CMTB patient lymphoblasts immunostained for Dynamin 2. The top panel shows control lymphocyte cells displaying a punctate-like pattern of staining and the bottom panel shows patient lymphocytes expressing the mutant Dynamin 2. In these cells the Dynamin 2 is clustering in large vesicular structures.

Approximately 15% of all CMT is inherited on the X chromosome. Dr Inken Huttner, a visiting research fellow from Germany, studied a large X-linked family, and mapped the disease locus to a 5.7 megabase interval on chromosome Xq26.3-q27.1 (CMTX3). Fourteen genes in the interval have been excluded for a pathogenic role in this family (Figure 2).
Hereditary sensory neuropathy type 1 (HSN1) is the most common form of peripheral sensory neuron degeneration. Clinically it is characterised by loss of pain sensation, muscle wasting and weakness. Mutations in the serine palmitoyltransferase long chain subunit 1 (SPTLC1) gene cause HSN1. Pilot studies over-expressing the mutant SPTLC1 gene in human neuronal cells showed altered localisation of the SPTLC1 protein and changes to the actin cytoskeleton. The laboratory has also developed an HSN1 mouse model.

Dr Stephen Reddel is currently undertaking research on the diagnosis of CMT neuropathy. His work, as yet in its early stages, involves the development of an immunohistochemical staining method to diagnose CMT using patients’ biopsies of sural nerve or skin.

Myasthenia Gravis
Dr Reddel also has a research interest in acquired myasthenia gravis, a condition which can cause a number of symptoms including eyelid drooping, double vision and changes in swallowing and speech. Myasthenia gravis is known to be associated with antibodies to two different proteins at the neuromuscular junction: acetylcholine receptor and muscle specific tyrosine kinase (MuSK). Dr Reddel’s work will look at how autoantibodies to MuSK affect the neuromuscular junction and contribute to myasthenia gravis.

Motor Neuron Disease
The genetic forms of motor neuron disorders range from severe progressive disease such as amyotrophic lateral sclerosis (ALS) that has affected Lou Gehrig and the famous astronomer Stephen Hawking, to slowly progressive forms such as hereditary motor neuropathy (HMN). The Concord researchers
hypothesise that common pathways causing motor neuron death could be involved with both the slow and rapid forms of the disease. The researchers have been studying both ALS families as well as families with hereditary motor neuropathy to identify gene mutations causing motor neuron disease. Over the past 10 years the laboratory has been recruiting families for genetic studies. The ALS database continues to be expanded and currently has more than 150 families available for study (Figure 3). The first gene discovered for familial ALS was the superoxide dismutase 1 (SOD1) gene. It is the most common mutation seen in about 10% of families. The researchers’ work has targeted SOD1 negative ALS families. These families have been expanded for linkage analysis and DNA results from spouses and children have been used to “reconstruct” the genetic information from deceased family members. Finding more genes causing motor neuron disorders may help to define pathways causing premature death of motor neurons and may lead to the development of new drugs to prevent and treat motor neuron disease.

Acknowledgements:
The peripheral neuropathy research was supported by an NHMRC grant to Professor Nicholson and Dr Kennerson from 2003-2005. Motor Neuron Disease research has been supported by the Amyotrophic Lateral Sclerosis Association USA (2003-2005), the MND Research Institute (2004) and the Australian Rotary Health Fund/Rotary Club of Caringbah (2005). The USA Muscular Dystrophy Association provided funding for construction and characterisation of a hereditary sensory neuropathy type I transgenic mouse study (2003-2005).
One of the primary roles for Occupational Therapists working in aged care is the assessment of a client’s home.

The main aim of the assessment is to review the client’s safety in their home environment. The Occupational Therapist will then make recommendations and implement strategies to enhance the client’s safety and function in this environment, and to minimise the likelihood of a fall.

**The Home Access Project**

In view of the labour intensive nature of home assessment, and the constant demand on health professionals to utilise limited resources in the most efficient manner, a project was recently conducted by Nicole Woodward (Occupational Therapist) and her colleagues, Gina Frampton and Sonia Gorman, at Concord Hospital. The occupational therapists who participated in this project worked within the General, Geriatric and Rehabilitation Medicine (GGRM) clinical stream.

Occupational Therapists from the community and hospital sectors collected data for six months for the purpose of the project. All clients referred to the service for home assessment were asked to participate in the project. Upon recruitment, the Occupational Therapists administered a questionnaire to the subject. The questionnaire was designed by researchers to determine the client’s perception of their ability to enter and exit their home.

The next step in the project was for the Occupational Therapist to conduct a home assessment with the subject. During this visit, the Therapist observed the client and assessed the client accessing their home as being unsafe or safe. This was done to allow comparisons to be made between the Occupational Therapist’s assessment of the client’s safety and the client’s own report. At this stage the Occupational Therapist also determined the modifications required to home access which would be needed to improve the client’s safety. Modifications included the installation of rails and ramps, and step alterations. The Occupational Therapist then made arrangements for the modification to be completed, if the client was agreeable.

Once the modifications were completed, the Occupational Therapist conducted another visit to the client’s home. During this visit, the Occupational Therapist re-assessed the client’s ability to safely enter and exit the home, utilising the modifications. The client completed a similar questionnaire with some additional questions related to satisfaction with the Occupational Therapy service also included.

Researchers have recently commenced data analysis and the interpretation of the results. It is anticipated that the project will be completed by the end of 2005. Researchers expect that this project will contribute valuable information to the Occupational Therapy profession in the area of home assessment, and assist practitioners to develop best practice guidelines for this role.
Rosemary Burke, director of the Pharmacy Department, was awarded a grant to carry out work aimed at improving medication safety and reducing adverse drug events in elderly hospitalised patients.

To evaluate the results, an adverse drug event rate needed to be measured. Many tools available for measuring adverse drug events are labour-intensive and involve disguised observer or retrospective review of the medical records. Part of this study investigated whether a quality methodology developed by the Institute of Healthcare Improvement (IHI) would provide an accurate, easy to use, reproducible means of detecting and tracking harm resulting from adverse drug events (ADE).

The tool uses “triggers” or “flags” in the medical notes that may indicate an adverse drug event has occurred. These triggers could be the addition of a drug, an abnormal laboratory result or an event such as a fall.

The reviewers assessed a random sample of 300 medical records for patients aged 65 years and older to test the applicability of this method. Rates of adverse drug events were then calculated and harm assessed using the National Coordinating Council for Medication Error Reporting and Prevention Index.

The researchers found that 31.3% of patients over the age of sixty-five had at least one ADE on admission or during their stay in the hospital. There were 3.10 ADE’s per 1000 doses of medication. These detected ADEs had either a temporary effect (86%) or a minor to moderate impact (14%) on the patient. None of the ADEs detected resulted in significant harm. The major drug groups involved were narcotics, antihypertensive medication and antibiotics. The results were similar to published data from the USA.

Records from 100 patients (not limited by age) were also reviewed. In this group, 18% of patients experienced an ADE and there were 2.21 ADE’s per 1000 doses. This difference was expected, as older patients tend to be on more medications and are at a higher risk of an ADE.

Quality improvement projects were then developed to improve the use of certain drugs in the hospital population.

Acknowledgement:
This research was funded by the Australian Council for Safety and Quality in health care via their Medication Safety Innovations grant.
Physiotherapists at Concord Hospital are undertaking important new research into two areas relevant to our ageing population.

**Investigating the effect of pulmonary rehabilitation on exercise capacity following lung resection**

Ms Yasmin Silva from the Department of Physiotherapy, Concord Hospital is collaborating with Dr Frank Li (Physiotherapist) and Associate Professor Matthew Peters (respiratory physician) to carry out a pilot study investigating the effect of pulmonary rehabilitation in patients who have had removal of part of their lung.

The treatment for certain types of lung cancer is the removal of lung tissue (lung resection). Studies show that lung resection decreases lung function to a similar level as that of patients with chronic obstructive pulmonary disease (COPD). Smoking is a major cause of COPD. Most lung cancer patients have a history of smoking. Pulmonary rehabilitation is offered to patients with COPD, but it is not currently being offered for patients who have had lung resection. This pilot study evaluated the effect of a four-week pulmonary rehabilitation programme on exercise capacity after lung resection.

Patients having lung resection via chest wall incision (thoracotomy) were invited to participate in this study. These patients were divided into two groups. Both groups were treated with breathing and mobility exercises whilst in hospital. Upon discharge from the hospital, the control groups were advised to mobilise and the exercise group participated in an individualised pulmonary rehabilitation programme, once a week for four weeks. The programme consisted of endurance exercises and weight training of moderate intensity. Patients were also prescribed a daily walking programme. Exercise capacity was measured using the Six Minute Walk Test (6MWT) - a measure of how far the patient can walk in six minutes. The 6MWT was performed on three occasions (pre surgery, on discharge and six weeks after surgery).

The 17 patients who completed the study included seven in the control group (mean age 65.86) and ten in the exercise group (mean age 63.20). Results of the 6MWT are listed in the table below.

<table>
<thead>
<tr>
<th></th>
<th>Pre Mean (range)</th>
<th>Discharge Mean (range)</th>
<th>6wk post Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control group</strong></td>
<td>398.00m (160–530)</td>
<td>275.43m (110–450)</td>
<td>342.71m (140–485)</td>
</tr>
<tr>
<td><strong>Exercise group</strong></td>
<td>425.60m (340–600)</td>
<td>265.10m (190–395)</td>
<td>441.50m (340–612)</td>
</tr>
</tbody>
</table>
Physiotherapy

When comparing the difference in the 6MWT from discharge to six weeks post surgery, there was a significant gain in the exercise group (p=0.01). Improvements in lung function were also observed in the exercise group but this did not reach a significant level.

The exercise group had a better 6MWT, six weeks after surgery compared to the pre surgery level. Participating in pulmonary rehabilitation appears to facilitate a faster recovery of exercise capacity. It is also possible that these changes could be due to either stopping or reducing smoking post surgery. The control group’s 6MWT after six weeks had still not reached their pre surgery level when compared to the exercise group. Thus this study raises the question of the potential benefit of exercise prior to lung resection. Pulmonary rehabilitation after lung resection appears to improve exercise capacity due to the training effects and the psychological benefits of exercise. The recommended guideline for pulmonary rehabilitation is three times a week for six weeks. A further improvement in exercise capacity may have occurred if pulmonary rehabilitation guidelines were adhered to or more aerobic activities were included.

Falls and balance control in the elderly and the effect of fatigue

People over the age of 65 are known to have an increased incidence of falls. One of the reasons for this is the decline in the balance control mechanism with age. Dr Frank Li from the Physiotherapy Department at Concord Hospital, in collaboration with researchers from the University of New South Wales, has undertaken biomechanical studies which indicate that in the elderly there are changes in their walking pattern (such as step length, amount of arm or leg swing, walking speed) and a decrease in muscle strength. Loss of muscle strength was strongly correlated with the incidence of falls.

In early 2005, a new study was commenced in conjunction with the Neurology Department at Concord Hospital. This study looked at patients with peripheral neuropathy (general weakness of muscles in the arms, legs and trunk). The study was funded by a grant of $4,200 awarded to Dr Frank Li by the Research Centre for Adaptation in Health and Illness (RCAIH). Subjects with peripheral neuropathy underwent force platform measurement, in which patients stand on a platform which records body sway (ie shifting of the centre of gravity). At the same time patients had electrodes placed on their back, thigh and calf muscles to record the electrical activity of those muscles (EMG recording). Subjects were then asked to exercise for 15 minutes and the recordings were repeated. Analysis of these results will allow researchers to investigate the changes in balance control and the contribution of muscles to balance control. As part of this study, the benefits of wearing an ankle brace (which may aid stability and balance) will also be investigated. This study will represent pioneering work in this area, as it is the first of its kind to be undertaken.
Radiological investigation is an important element in a number of research activities currently being undertaken at Concord Hospital.

The Department of Radiology has been involved in a number of collaborative projects, including studies on ageing and dementia with the Centre for Education and Research on Ageing (CERA). Recent studies have looked at the relationship of the size of the hippocampus (a region in the brain) with various measures of memory. The studies have shown a correlation between the volume of this part of the brain with memory function, such as delayed retention of verbal material, even in elderly people who were otherwise well. Another paper demonstrated that lesions in the white matter of the brain are common in the very old. However these were not necessarily an indicator of a cognitive decline.

Other successful collaborations include studies with the Departments of Nuclear Medicine, Orthopaedics and Rheumatology on conditions such as avascular necrosis of the talus after minor trauma (a condition in which poor blood supply leads to bone death in the ankle) and acetabular labral tears in young patients with hip pain (tears in the lining around the rim of the hip socket).

Radiologists remain closely involved with the oncologists in the evaluation of new chemotherapy drugs and in treatment (such as evaluating radiological insertion of devices to administer chemotherapy to cancer patients). In conjunction with the vascular surgeons, different types of endoluminal treatment of aneurysms have been assessed. Thoracic medicine and surgery collaborations include assessment of virtual bronchoscopy as an aid to diagnosing airway lesions. Multidetector computerised tomography (a minimally-invasive technique to image the heart and coronary arteries) has developed as a major area of interest for both the Radiology and Cardiology departments. Studies show the value of this newly emerging technique, and provide further insight into coronary artery disease.

In recent years the Radiology Department has initiated new areas of research that have received national recognition. At the College of Radiology’s Scientific Meeting in 2003, Dr Morris received a commendation for his poster on assessment of complications of endoluminal repair of aortic aneurysms. In 2004 Dr Sum was runner up in the category of best paper by a junior radiologist for work carried out in collaboration with the Cardiology Department of Concord Hospital. She presented a paper evaluating the relationship between computerised tomography (CT) and echocardiographic assessment of cardiac function. Other highlights at this conference included Dr Dunn’s 4-year retrospective review of all cases of air in the biliary tree, which refuted a previously accepted sign.

The major achievement was the awarding of the Royal Australian and New Zealand College of Radiology and the International Radiology Quality Network prize for best poster to Dr Faisal Rashid (right) for his poster on “Protocols for Exposure to Ionising Radiation During Pregnancy”. This poster discussed the risks and benefits of imaging in pregnancy, and methods to reduce exposure in high-risk patients.

The Radiology Department anticipates that its research activities will continue to expand in coming years. Already there is extensive interest in performing collaborative studies using the new, state of the art, 3.0 Tesla Magnetic Resonance Imaging (MRI) scanner that has recently been installed in the department – the first of its kind in a public hospital in Australia.
In 2004, Leigh Seccombe, respiratory scientist, and her colleagues in the Department of Thoracic Medicine, undertook research which looked at the possible effects of commercial flight on oxygenation in patients with lung disease.

The researchers looked at patients suffering from two types of lung disease. Chronic Obstructive Pulmonary Disease (COPD) is a lifelong inflammatory disorder of the lungs most commonly resulting from smoking. COPD is characterised by difficulty breathing, wheezing and a chronic cough. Interstitial Lung Disease (ILD) is the collective term for a group of disorders characterised by inflammation and scarring (fibrosis) of lung tissue and causing cough and shortness of breath. Our ageing population has an increased rate of these types of lung disease. Yet many of this population are undertaking commercial air travel on both short and long-distance flights.

The question of whether flight is safe for patients with lung disease arises frequently. Commercial aircraft are required to be pressurised to a cabin pressure equivalent to 8,000 feet under normal operating conditions. This pressurisation results in a fall in arterial oxygen pressure in normal people, and it is well documented that this fall is accentuated in patients with COPD. However the data for hypoxaemia (low oxygen content in arterial blood) in aircraft passengers with ILD have been lacking.

The researchers simulated conditions of flight in a commercial aircraft by asking participants to breathe a hypoxic gas mixture containing 15% oxygen. A modest exercise stress test was also included (walking 50 metres on a treadmill) to further simulate conditions during flight. Arterial blood gas samples were taken during the procedure.

Fifteen patients with ILD and ten subjects with COPD were tested. At sea level, all of the subjects had acceptable arterial blood gas levels. However, after cabin altitude simulation, subjects in both groups suffered a significant drop in arterial oxygen levels. This drop was exacerbated by the 50-metre walk test, after which the majority of participants fell below an acceptable level of oxygenation. In both groups, it appears that resting sea level arterial blood gas tensions were a poor predictor of response to simulated cabin altitude.

Despite the severe hypoxaemia observed during the simulation test, about half the patients in the study had flown in the last two years without suffering an acute adverse event during flight. The researchers concluded that further prospective evaluation of a large number of patients with lung disease who plan to fly, would be required in order to provide more information about potential hazards for these patients during commercial flights.
Urinary symptoms and prostate cancer are common conditions encountered in the ageing population. The Urology Department at Concord Hospital has a major research interest in the changes of the bladder associated with ageing.

The Detrusor ultrastructure research project, co-ordinated by Dr Lewis Chan, has been investigating the cause of overactive bladder syndrome (frequency, urgency and urge incontinence) as well as response of the bladder to outlet obstruction due to benign enlargement of the prostate. A recent study by Dr Ruth Collins looking at patients with urinary retention identified specific degenerative changes in the bladder muscle, which can help in predicting patients who may benefit from prostate surgery (see Figures 1 and 2).

Prostate cancer affects up to one in ten men in their lifetime. Many men with prostate cancer initially present with an elevated PSA (prostate specific antigen) blood test or abnormal digital rectal examination. The diagnosis is usually established by transrectal ultrasound guided prostate biopsy. Dr Tze Kiat Ng (a visiting registrar from Singapore) and Dr Andre Lalak reviewed the prostate cancer database of 2,800 patients who underwent prostate biopsy at Concord Hospital and established a nomogram which helps men estimate their risk of prostate cancer based on the rectal examination and PSA results. This is the largest study of its kind in Australia and provides valuable local information for men who are found to have an elevated PSA.

![Figure 1](image1.png)

**Figure 1**
A microscopic view of the normal bladder showing muscle cells neatly arranged in fascicles.

![Figure 2](image2.png)

**Figure 2**
A microscopic view of the bladder of a patient with chronic urinary retention showing features of muscle cell degeneration with shrivelling and fragmentation of cells, and increased spaces between cells.
Much of the research carried out at Concord Hospital is supported by the staff and services of the Concord Hospital Medical Library. Library staff ably assist in bridging the gap between research efforts and the literature through the provision of current awareness services, mediated literature searching, document delivery, and user education.

The professional searching skills and knowledge of Library Reference staff enable them to carry out subject oriented literature searches across both print and electronic resources, providing research clients with relevant information on demand. As well, utilising both onsite and external sources - including the depth of Australia’s health libraries and the extensiveness of the National Distributed Collection - this small group of information professionals source material for researchers as required, quickly and without charge.

Central to the provision of services and the first port of call when sourcing information is the Library collection itself, which includes over 5,000 monographic titles, more than 1,000 print and electronic journal and monographic series titles (including a number of unique local holdings) numerous health-related annual reports, conference proceedings and Royal Commission reports. This collection, with its ever growing number of electronic resources and print titles, continues to provide a huge support base for the research effort at Concord.
Clinical Trials Pharmacy Unit

The primary aim of the Concord Hospital Clinical Trials Pharmacy is to optimise patient outcomes by working to achieve the best possible use of investigational drugs.

The unit is staffed by Lucy Nigro (Clinical Trials Pharmacist) and Helen Sanders (Clinical Trials Assistant).

One of the specific objectives of the Clinical Trials Pharmacy is to support and promote medical and pharmacy research. This is achieved in several ways.

The unit provides assistance in preparation of submissions to the Concord Hospital Drug Committee and the Concord Hospital Ethics Committee. This includes co-ordinating the reporting of serious adverse events. The unit is also responsible for providing advice on changes in relevant legislation and procedural matters (e.g. Therapeutic Goods Act and Regulations, Special Access Scheme). The unit's staff members liaise with the pharmaceutical industry to assist in the procurement of clinical trial drugs and other investigational drugs. This sometimes includes importing the drugs from overseas.

The Clinical Trials Pharmacist gives advice on study design and/or protocol development. The unit is also responsible for developing randomisation schedules and placebos for investigator initiated in-house studies and ensuring that accurate and comprehensive pharmacy records are maintained for clinical drug trials.

The Pharmacy department provides aseptic reconstitution facilities.

In 2004 and 2005, 70 new clinical trials of investigational drugs were approved for conduct at Concord Hospital. These included new drugs for the treatment of a wide range of disorders in the areas of Andrology, Cardiology, Endocrinology, Gastroenterology, Geriatric Medicine, Haematology, Intensive Care, Neurology, Respiratory Medicine, Rheumatology, Urology and Medical Oncology. The Concord Clinical Trials Pharmacy Unit is currently responsible for administering and dispensing for approximately 80 active drug trials.
For a comprehensive summary of research projects carried out at Concord Hospital 2004/2005 and a list of key publications, please visit the Concord Research Office website at: