ROYAL AUSTRALASIAN COLLEGE OF SURGEONS

John Mitchell Crouch Fellowship

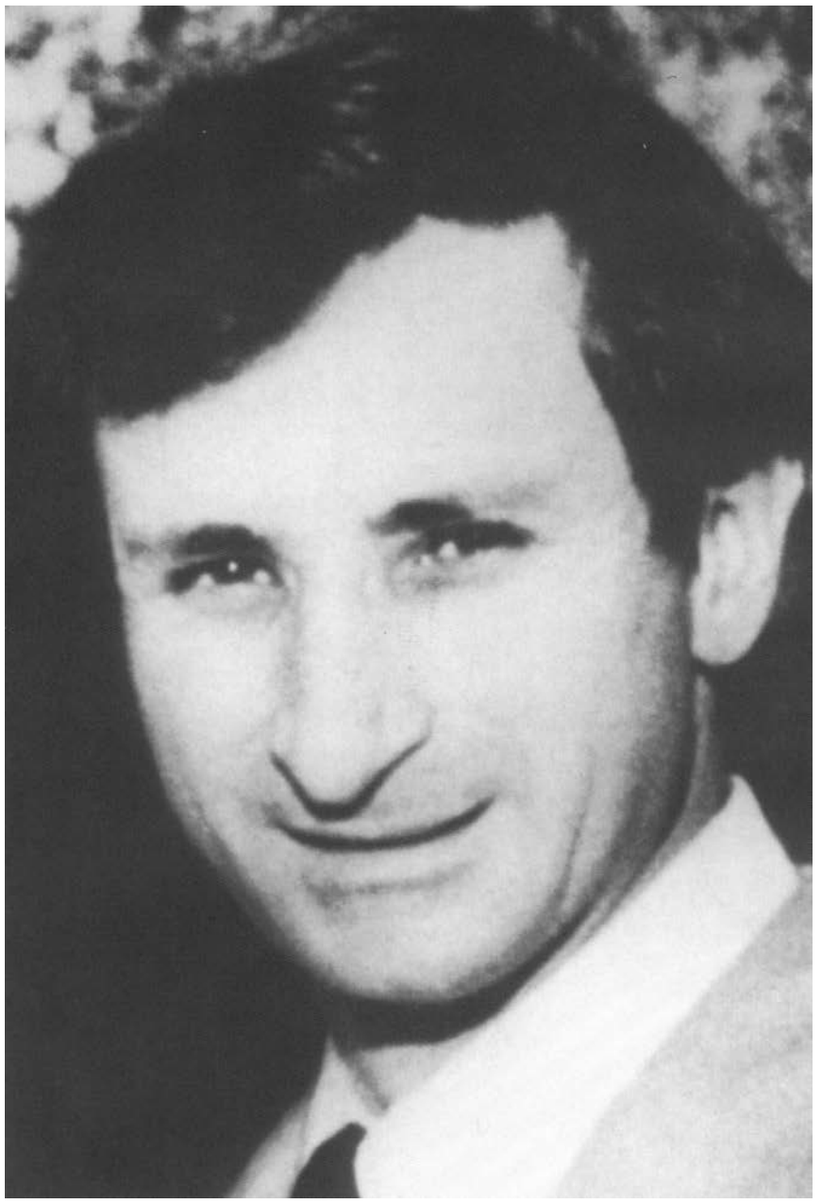
1979-2014

John Mitchell Crouch Fellowship

The John Mitchell Crouch Fellowship is the premier research award of the Royal Australasian College of Surgeons. It was first awarded in 1979.

The Fellowship was initially awarded annually to an individual who, in the opinion of the Council of the College, was making outstanding contributions to the advancement of surgery or anaesthesia or to fundamental research in these fields. In more recent years the focus has been solely on surgical advancements and research.

The Fellowship is available to Fellows of the Royal Australasian College of Surgeons or surgeons with comparable overseas qualifications, who are resident in Australia and New Zealand.



John Mitchell Crouch

The John Mitchell Crouch Fellowship commemorates the life and work of John Mitchell Crouch who was born in Bristol, England on September 13, 1940.

His early life involved a good deal of travel with his parents and education in England, Europe and Africa. In 1954, following the accidental death of his father in Africa, he moved with his mother to Australia.

Even at this young age, he showed himself to be gifted with many talents. While obtaining excellent results in his studies, he also developed his interests in music, art, the theatre and he excelled in a number of different sports.

John Mitchell Crouch matriculated from Wesley College, Melbourne in 1959, studied Medicine at the University of Melbourne and St Vincent's Hospital Clinical School, was a resident at Queens College and graduated in 1966. His post-graduate training included posts at Preston and Northcote Community Hospital followed by an intensive post-graduate program at the University of Toronto, Canada.

John Mitchell Crouch worked in major hospitals including the Hospital for Sick Children and Toronto East General. In 1972 he became a Fellow of the Royal College of Physicians and Surgeons of Canada and licentiate of the Canadian Medical Council. He earned the distinction of being appointed Chief Resident Surgeon at Toronto General Hospital.

John Mitchell Crouch's special interest in Neurosurgery subsequently led him to accept appointment as Clinical and Experimental Research Fellow in Neurosurgery at the Hospital for Sick Children.

Despite offers of senior Neurosurgical appointments in Toronto and Sydney, he accepted in January 1974 the challenge of appointment as Honorary Surgeon and first Medical Director at the Frankston Community Hospital, Victoria. In a very short period of time his energy, innovative thinking and leadership qualities enabled him to make a major impact on the clinical and administrative activities at that hospital. He also became a Fellow of the Royal Australasian College of Surgeons in 1974.

Regrettably, his skills and very promising career were not permitted to blossom. In 1975 he became seriously ill with a brain tumour. He underwent surgery on several occasions, facing his cruel illness with great fortitude. He finally died at home in Sydney on January 28, 1977.

The John Mitchell Crouch Fellowship was established by Mrs Elisabeth Unsworth in honour of her son in the hope that recipients would contribute to the understanding and practice of Surgery and Anaesthesia in keeping with the skills and promise so ably demonstrated by John Mitchell Crouch during his all-too-short professional career.

John Mitchell Crouch Fellowship

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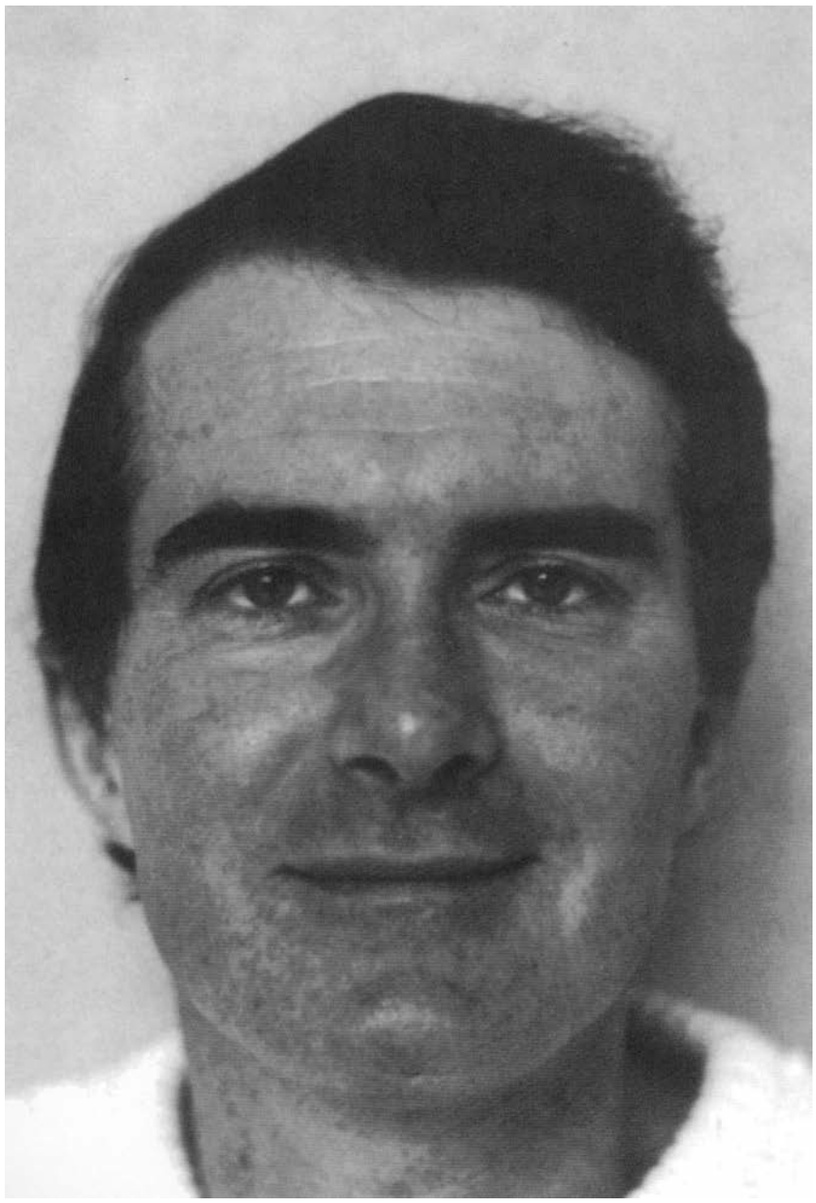


1979

Robert Charles Burton

Professor of Surgical Science, University of Newcastle

The John Mitchell Crouch Fellowship supported Professor Burton in 1980 for a year of research into transplantation and tumour immunology at the Transplantation Unit of the Massachusetts General Hospital, Harvard University in Boston, USA. Professor Burton studied the regulation of T (thymus derived) lymphocyte immune responses against kidney and heart transplants in mice and kidney transplants in monkeys, and collaborated in the first treatment of renal transplant rejection in humans with monoclonal antibodies. Subsequently immune monitoring by monoclonal antibodies of renal transplant patients for detection of transplant rejection and infection was studied.

The treatment of transplant patients with monoclonal antibodies which destroy all T lymphocytes is now an important part of therapy in clinical transplantation, and these pioneering studies defined most of the advantages and drawbacks of treatment. In particular, it was shown that patients can make a vigorous immune response against monoclonal antibodies made in non-human species. Further studies demonstrated that mouse monoclonal antibodies directed at only a subset of T lymphocytes could prevent renal transplant rejection in monkeys. This treatment is currently being tested in humans. The immune monitoring studies established the utility of this technique in the diagnosis of infection and for adjusting the dosage of certain immunosuppresive drugs in transplant patients. Immune monitoring is now also used worldwide in the management of AIDS and other infectious diseases.

Professor Burton's cancer studies resulted in the discovery of some of the first specific markers of cells in mice which can destroy certain types of cancers. These markers identified subsets of these natural killer (NK) cells, and it was subsequently shown that one of these subsets was important in preventing certain infections and the metastasis of sarcomas and melanomas in mice.

Other studies, commenced at that time, have shown that NK cells mediate resistance against certain bacterial, viral and protezoal infections in mammals. and play a role in the normal regulation of mammalian haematopoiesis. Finally, studies with a certain NK markers definitively demonstrated that subsets of NK cells exist which have different functions in resistance to cancer. One of these subsets, natural cytotoxic (NC) cells, was shown to be important in resistance against chemical carcinogenesis in mice.

These studies resulted in publications in the New England Journal of Medicine, the Journal of Experimental Medicine, the Journal of Immunology and Transplantation and to Professor Burton's promotion in 1981 to Assistant Professor of Surgery at Harvard University. In November 1981, Professor Burton returned to Australia as the Foundation Professor of Surgical Science at the University of Newcastle.

1980

JOHN FREDERICK FORBES

Professor of Surgical Oncology, University of Newcastle

The John Mitchell Crouch Fellowship of the College awarded to Professor Forbes played a substantial role in the establishment of the Australian New Zealand Breast Cancer Trials Group (ANZ Group). A research initiative in 1978 led to a multi-centre prospective randomised trial to compare endocrine treatment (Tamoxifen in postmenopausal women, surgical oophorectomy in premenopausal women) with cytotoxic chemotherapy or combined modality therapy as first line treatment for women with advanced breast cancer. At the time, cytotoxic chemotherapy was becoming widely used throughout the world as first line treatment for these women.

The ANZ Group was established with its central data managers and network of computers in the Department of Surgery at Royal Melbourne Hospital (strongly supported in turn by Professors Maurice Ewing and Gordon Clunie). The Group was co-ordinated by Professor Forbes and the trial – a new venture for many surgeons and other colleagues – proved to be a major learning experience for all involved. This clinical trial became one of the largest and most important conducted and established the credibility of the Group internationally. It showed that although the response rate to Tamoxifen as first treatment was inferior to the response rate with cytotoxic chemotherapy, ultimate survival was not compromised, and side effects and quality of life were more acceptable with the Tamoxifen. The trial has had a major influence on the treatment of breast cancer throughout the world and on the conduct of clinical trials in Australia and New Zealand.

The trials' national Operations Office was relocated to the new Department of Surgical Oncology at the Newcastle Mater Misericordiae Hospital in the University of Newcastle in 1987, and Professor Forbes has continued to co-ordinate the trials. The ANZ Breast Cancer Trials Group has gone on to further substantive research activities and now co-ordinates national treatment evaluation programs for all stages of breast cancer. The Group has had continuous NHMRC support since 1979.

Seven adjuvant breast trials have now been completed with international collaboration via the International Breast Cancer Study Group and these have made major contributions to the recent international overview of all trials. Current trials now involve advanced disease, in situ cancer, and a new initiative for breast cancer prevention to be extended nationally in 1993. Thus, the John Mitchell Crouch Fellowship helped create what has now become a national resource committed to the control of breast cancer and which now involves many members of the Royal Australasian College of Surgeons.

1981

Bruce Nathaniel Gray

Professor of Surgery, Royal Perth Hospital
Medical Director, Lions Cancer Institute, Perth

The John Mitchell Crouch Fellowship was awarded at a time when Professor Gray was promoting co-operative clinical trials of adjuvant therapy in bowel cancer. The award of the Fellowship was used primarily to promote two areas of research at the Department of Surgery at St Vincents Hospital, Melbourne. However, the Fellowship was also used to promote a number of smaller but related cancer research projects.

The Australia and New Zealand Bowel Cancer Trials that were supported by the Crouch Fellowship were assessing the role of adjuvant portal vein chemotherapy in colon cancer and adjuvant radiotherapy in rectal cancer. These clinical trials recruited patients from throughout Australia and New Zealand and have made a significant contribution to understanding the value of adjuvant treatment in bowel cancer. In 1992 a meta-analysis for all studies in the world in which portal vein chemotherapy has been used was undertaken. The Australia and New Zealand trial was one of the major studies in this large meta-analysis which has shown a significant improvement in survival for patients treated by this new form of therapy.

These Australia and New Zealand Trials were the forerunner of much larger scale co-operative trials in Australia and New Zealand for the treatment of gastrointestinal malignancy. The recently formed Australasian Gastrointestinal Trials Group has taken over the role of the Australia and New Zealand Bowel Cancer Trial that was initially promoted using assistance from the Crouch Fellowship.

The second major project that the Crouch Fellowship was used for, was to investigate the use of internal radiotherapy using radioactive microspheres in the treatment of disseminated liver malignancy. This has been a major project that has been actively pursued since that time. Royal Perth Hospital is now a centre for the use of Internal Radiation using radioactive microspheres for the treatment of liver cancer. This project has been refined constantly since it was initiated in 1981 and the technology has now been exported to a number of other centres that are commencing similar programs.

Since 1981 Professor Gray has actively pursued an academic career with research being a major component of those activities. He relocated to Royal Perth Hospital in 1985 where he was appointed Professor of Surgery in the University of Western Australia. In 1990 he was appointed Medical Director of the Lions Cancer Institute in Perth. This institute is an expanding research base devoted to investigating the causes and treatment of cancer.

1982

Michael John Cousins

Professor & Head of Department of Anaesthesia, University of Sydney
Professor and Head of Department of Anaesthesia and Pain Management, Royal North Shore Hospital

1. Metabolism and toxicity of inhalation anaesthetic agents

These studies involved collaboration with a pathologist (Associate Professor Pauline Hall), a surgeon (Professor P. O'Brien), a morphologist (Dr C. Lunam), pharmacologists (Dr J. Plummer and G. Gourlay) and four research students completed their theses in the course of the project.

In a clinical study, evidence was provided that anaesthesia with halothane is frequently associated with transient but significant impairment of liver function, in association with the reductive metabolism of halothane. In this randomised prospective controlled study, such changes were minimal or absent with other anaesthetics. In a series of interlocking basic studies, in a rat model and also a guinea pig model, it was confirmed that halothane has a greater potential to cause liver injury than the more recent inhalation anaesthetic isoflurane. These studies helped to confirm risk factors which had been proposed, based on clinical epidemiological evidence: repeated anaesthesia, age, sex, familial susceptibility. In controlled studies of chronic exposure to trace concentrations of anaesthetics, only halothane had a potential for liver damage. Interestingly, studies of related halogenated hydrocarbons revealed the importance of exposure profile and revealed a potential interaction with alcohol to produce persisting liver damage.

In the very rare cases of massive hepatic necrosis following halothane anaesthesia, other groups have now provided evidence that the oxidative metabolism of halothane may be associated with the formation of a hapten which elicit an immunologic response. It still seems likely that a genetically determined susceptibility may play a part. In Professor Cousins' group's guinea-pig model, halothane was associated with severe liver injury, but only in some animals. This lesion appeared to be associated with oxidative rather than reductive metabolism. Subsequently it was demonstrated there was an inherited susceptibility in this guinea-pig model and a detailed description of the ultrastructure and gross pathology of the hepatic lesion was provided. The guinea-pig model has now formed the basis of studies which have demonstrated the immunologic component of massive hepatic necrosis following halothane anaesthesia.

2. Treatment of cancer pain with opioids via oral and spinal routes

During the tenure of the Fellowship, a randomised prospective controlled study examined the oral use of the short acting opioid morphine compared to the longer acting drug methadone.

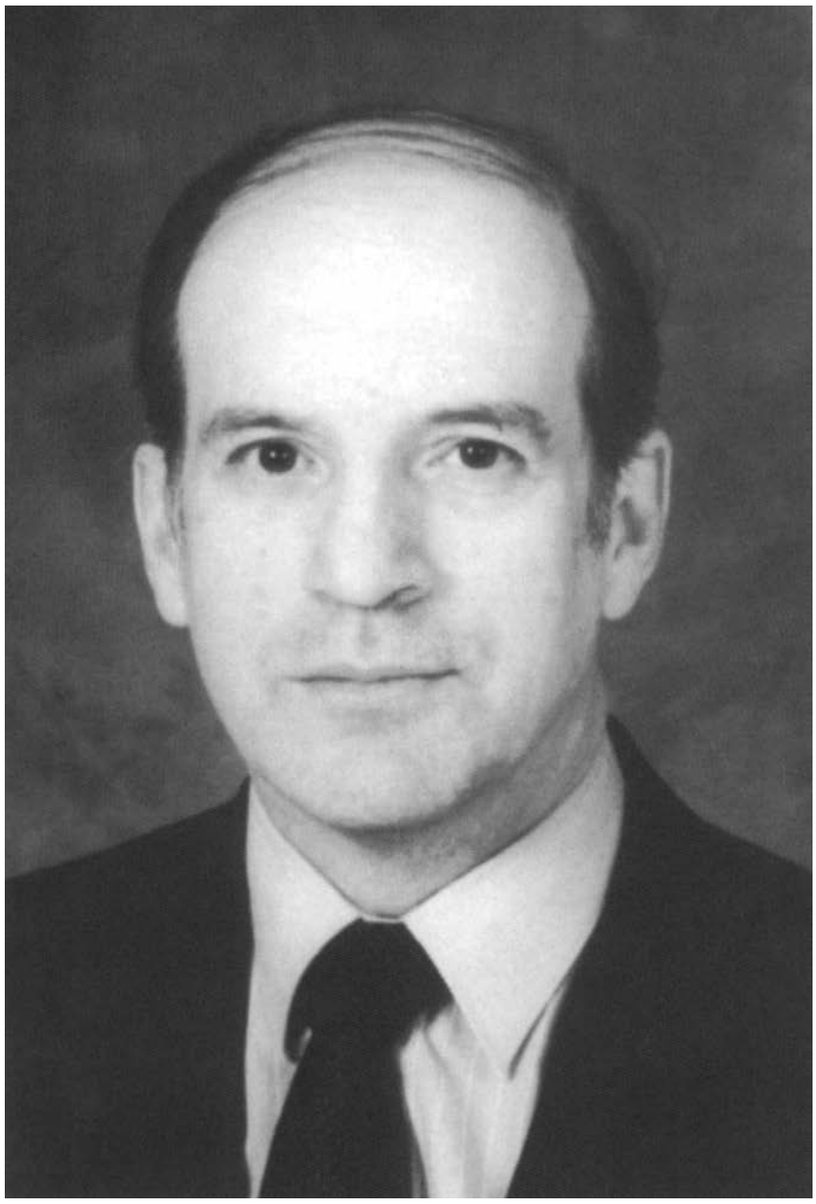
Pharmacokinetic data provided a sound basis for oral dosing and dosing intervals. As expected, the oral bioavailability of methadone was very high (mean 79%), whereas that of morphine was relatively low (mean 26%).

In the case of morphine there was a very large variability (range 10-43%) in oral bioavailability, providing an explanation for the clinical observation that some patients require oral doses which are much larger than intramuscular doses (3-6 times), while other patients require oral doses that may be in the range of one to two times that intramuscular dose. Another important finding was the brief durations of morphine analgesia, necessitating dosage intervals with morphine as small as 2.5 hours.

Follow-up of patients until death revealed that the large majority of patients maintained stable dosage requirements, provided very effective pain relief was obtained initially. Also a sudden increase in analgesic dosage requirements was invariably associated with the development of further metastases. This finding has subsequently been confirmed in studies by other groups. Studies of methadone pharmacokinetics in 162 cancer patients showed very large variability in half life and clearance amongst patients. This indicated a need for careful adjustment of dosing intervals in order to avoid the possibility of dangerous accumulation of the drug. Indeed the extremes of dosing interval varied from as little as four hours to as much as five days.

Patient and concurrent therapy factors were identified, which may influence the dosing interval' concurrent therapy with phenytoin, spironolactone, verapamil or oestrogens enhances methadone clearance and indicates that larger methadone doses or a shorter interval are required; in contrast concomitant use of amitryptyline and patient age greater than 65 years tends to be associated with a lower clearance rate and thus a requirement for longer dosing intervals and possibly smaller methadone doses. A practical blood sampling regime was developed which could be implemented on an outpatient basis for estimation of methadone pharmacokinetics, as an aid to optimising the use of this drug.

A series of interlocking studies of the blood and cerebrospinal fluid pharmacokinetics of opioids administered by the spinal route, provided a rational basis for the spinal use of these drugs in patients with cancer. The relatively water soluble drug morphine, was shown to distribute very widely over the spinal cord, thus recommending its use in diffuse cancer. In contrast, the lipid soluble drug Fentanyl was more restricted in its CSF distribution, thus making it more suitable for more limited areas of analgesia.



1983

William Geoffrey Cole

Head, Division of Orthopaedic Surgery, Hospital for Sick Children, Toronto
Professor of Surgery, University of Toronto

The John Mitchell Crouch Fellowship provided the opportunity to develop some innovative approaches to the characterization of mutations producing abnormalities of the musculoskeletal system. The research focused on the molecular biology of the collagens in children with genetic disorders such as osteogenesis imperfecta, Ehlers-Danlos Syndrome, Marfan's Syndrome and the chondrodysplasias.

The research program resulted in the characterization of many new mutations of collagen in osteogenesis imperfecta, several forms of the Ehlers-Danlos Syndrome and in some of the chondrodysplasias. The results showed that the mild forms of osteogenesis imperfecta were due a reduced amount of normal Type 1 collagen, whereas the severe forms were due to a deficiency of normal Type 1 collagen and the presence of mutant Type 1 collagen. The biochemcial results have had a major impact on the diagnosis and classification of osteogenesis imperfecta. The results have also enabled new treatment strategies to be developed. It is quite likely that methods of treatment that will result in an increase in bone mass in the mild forms of osteogenesis imperfecta will also be effective in the early treatment of patients with idiopathic osteoporosis.

Characterizing mutations in osteogenesis imperfecta and in the Ehlers,Danlos Syndrome have been relatively straightforward because the mutations are expressed by dermal fibroblasts. In contrast, little progress has been made in defining mutations of connective tissue genes that are specifically expressed in cartilage and bone because of the difficulty of obtaining suitable tissue samples. However, this research has shown that a skin biopsy or a sample of blood can be used for these studies. Dermal fibroblasts and peripheral lymphocytes transcribe, at a low level, genes that are normally considered to only be expressed in specific tissues such as bone and cartilage. As a result, it has been possible in this research to successfully characterize mutations involving cartilage specific collagens using skin biopsies and blood samples.

These research projects were undertaken in the Connective Tissue Research Unit of the Department of Orthopaedic Surgery at the Royal Children's Hospital in Melbourne and Department of Paediatrics at the University of Melbourne when Professor Cole held the position of Associate Professor of Surgery and subsequently Foundation Professor of Orthopaedic Surgery at the University of Melbourne and Chief Orthopaedic Surgeon at the Royal Children's Hospital in Melbourne. In 1992, Professor Cole was appointed Head of the Division of Orthopaedic Surgery at the Hospital for Sick Children in Toronto and Professor of Surgery at the University of Toronto. His clinical practice focuses on major congenital and genetic anomalies of the musculoskeletal system and is coupled to basic research of the molecular pathology of these disorders.

1984

GRAHAM LANCELOT HILL

Professor and Head, Department of Surgery,
Auckland School of Medicine

1. Understanding Metabolic Care

The metabolic management of patients undergoing major surgery has been studied by the research team in the University Department of Surgery at Auckland Hospital. Using a combination of in vivo activation analysis and dual energy X-ray absorptiometry the molecular composition of the bodies of more than 700 subjects in health and disease has been studied. By measuring the changes in body composition after surgery and evaluating perioperative energetics the metabolic management of patients undergoing major surgery has been clarified. Postoperative fatigue, skeletal muscle function, psychological function and the phases of convalescence have also been described in patients recovering from major gastrointestinal surgery and the results have given surgeons a better understanding and a more rational basis for perioperative care. Studies of the special metabolic problems encountered in septic patients, elderly patients, jaundiced patients and patients with massive weight loss presenting for major surgery have also been conducted.

2. Understanding Nutritional Care

The research team has also undertaken extensive investigations of malnourished surgical patients. They have developed definitions, studied the concept of critical weight loss and defined the types of malnutrition that occur in surgical patients. The disorders of body composition, metabolism and physiologic function that accompany malnutrition in surgical patients have been defined. Metabolic, physiologic and pharmacologic effects of nutritional therapy, both enteral and parenteral, have also been studied and the cost benefit of these expensive treatments has been clarified. Studies of the assessment of nutritional status, studies of nutritional requirements and clinical trials of enteral and parenteral nutrition have also been conducted.

3. Metabolism and Nutrition in Surgery of the Alimentary Tract

Studies of patients undergoing major gastrointestinal surgery have also been undertaken by the research team. Patients presenting with intestinal obstruction, inflammatory bowel disease, massive intestinal resection, enterocutaneous fistulas, and surgically created metabolic and nutritional problems have undergone extensive metabolic and nutritional investigation.

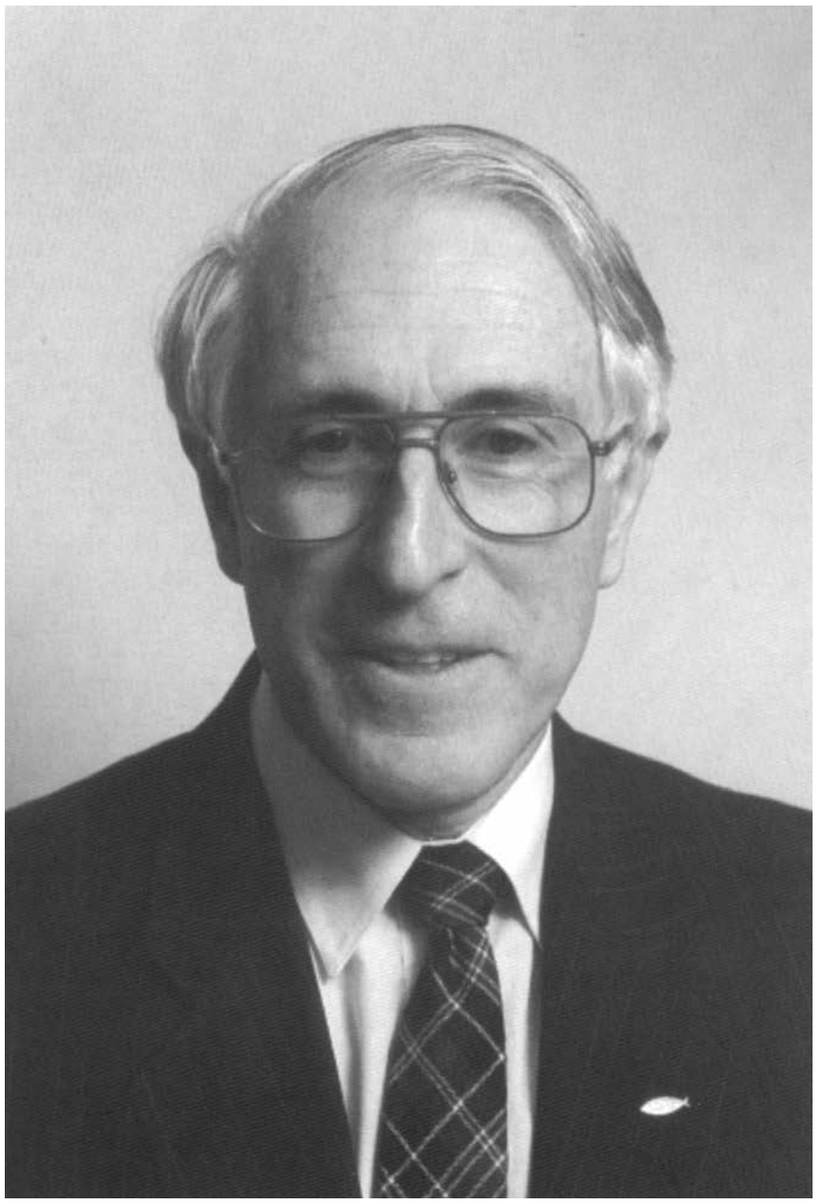
As a result, the practical metabolic and nutritional management of such patients has been described and presented in a systematic manner. The results of studies of perioperative nutrition have been presented and these have contributed to the worldwide consensus on how such patients should be treated.

4. Metabolism and Nutrition in Serious Surgical Illness

Metabolic and nutritional management in surgical intensive care patients has been studied, using the unique research facilities of the University Department of Surgery at Auckland Hospital. In general, standard nutritional therapy given to critically ill patients has been shown to be only partially effective and the team have developed new techniques for the testing of alternative strategies for the metabolic and nutritional management of critically ill patients. These include trials of nutrients which have been designed to act as a pharmacologic agents (to preserve physiological and immune function and promote wound healing), immunotherapy using monoclonal antibodies against endotoxin, and tumour necrosis factor (to lessen the impact of massive cytokine release), and the study of the efficacy of growth factors in aiding recovery and shortening convalescence after major trauma and sepsis.

5. Publications

The research described above has substantially benefited from the John Mitchell Crouch Fellowship Award. The clinical studies, which over a 10 year period have resulted in numerous publications in International Journals, have been brought together in a recently published monograph "Disorders of Nutrition and Metabolism in Clinical Surgery – Understanding and Management", Graham L Hill, Churchill Livingstone, Edinburgh 1992, pp324.



1985

Graeme Milbourne Clark

Professor of Otolaryngology, University of Melbourne

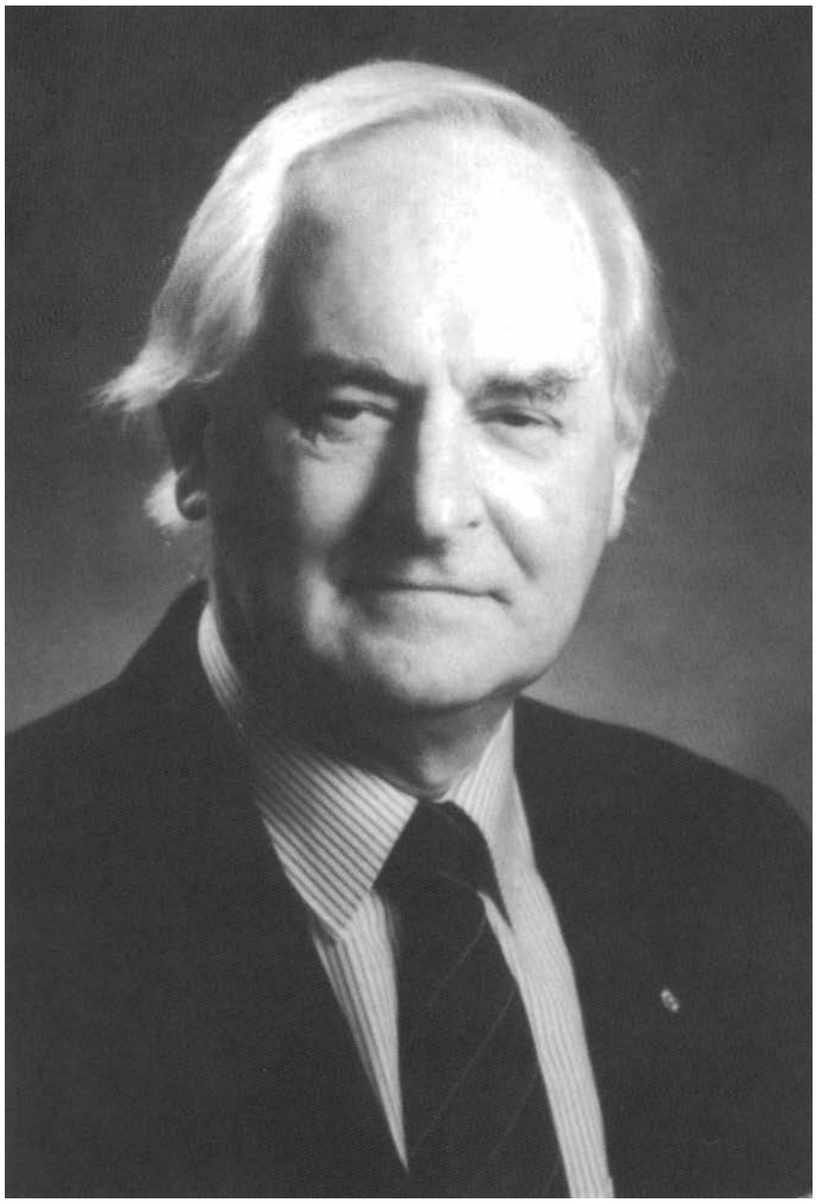
The cochlea, or inner ear, is a delicate structure, and an electrode array to stimulate residual hearing nerves electrically needs to be inserted so that vital structures are not damaged. Part of the funds received from the John Mitchell Crouch Fellowship went to establishing the optimal methods for carrying out the surgery safely.

The Crouch Fellowship funds also enabled Professor Clark's team to section and study the temporal bones of an implant patient who had died from unrelated causes. This provided valuable data to confirm that the electrode insertion could be carried out atraumatically, and that the electrical stimulus parameters used did not lead to the loss of the nerves and spiral ganglion cells it was hoped to excite. Another important finding was that the electrode array lay at the periphery of the cochlear spiral, and not close to the neutral elements at the centre.

To establish the benefits of placing electrodes more centrally, a series of physiological studies has been carried out and the effects of electrode placement have been monitored by recording brain stem electrically evoked responses. This research has suggested that the present electrode could be redesigned, with benefits to patients in the future.

To further study this issue, detailed measurements have been made of the dimensions of the human cochlea and those of certain experimental animals to determine how the animal experimental work can be best applied to humans.

Finally, funds from the John Mitchell Crouch Fellowship have been used to determine whether infection in the middle ear is likely to spread to the inner ear post-implantation. Middle ear infections are common in young children and infection spreading to the inner ear could have serious consequences. Professor Clark's research has, however, been able to show how the spread of infection can be prevented, and this has opened the way for carrying out cochlear implants in young children.



1986

Bernard McCarthy O'Brien

Director, Microsurgery Research Centre,
St Vincents Hospital, Melbourne

The John Mitchell Crouch Fellowship greatly contributed to the continuing research program at the Microsurgery Research Centre, St Vincent's Hospital, where multiple projects broadly related to reconstructive microsurgery have been conducted over several years.

The Microsurgery Research Centre was established in the late 1960's by Mr Bernard O'Brien to link the newly emerging field of clinical microsurgery with a scientific basis. Basic understanding of the pathophysiology of small blood vessels following microvascular anastomosis was investigated so as to perfect anastomotic techniques for replantation and free tissue transfer. Since that time a broad spectrum of scientific studies has been pursued involving many cross disciplines. The work has attracted continuing NH&MRC support since its inception. A training fellowship program was established in 1972, which has attracted in excess of 150 Fellows and visitors from all corners of the globe. Currently the Centre has a full-time staff of 26 medical and scientific personnel.

The projects specifically aided by the Fellowship included:

1. Studies in microvascular repair
The basis of survival of all tissue transfer is patency of small vessels. Commonly in replantation, avulsion injury prevents successful anastomosis and studies into the pathophysiology of avulsed vessels have demonstrated a surprisingly extensive pattern of injury which can now be predicted and utilised to make clinical transfers more reliable. Venous allografts of rabbit femoral vessels using short term cyclosporine remained patent for four weeks, which is sufficient to allow a tissue transfer on these vessels to establish an independent circulation by ingrowth from the surrounding tissues. Cessation of the cyclosporine allowed continuing free flap survival.

2. Ischaemia and reperfusion injury
Ischaemic skin flaps were studied in the rabbit and the role of prostacyclin, a potent vasodilator drug, in enhancing their survival. Flap ischaemia and drug protection has been an ongoing core research program at the Centre.

3. Tissue expansion
The expansion of skin flaps and their subsequent transfer as free flaps was investigated studying the alteration in the skin thickness and histological characteristics and the long term size gains.

4. Lymphoedema

Early studies by Mr Bernard O'Brien on lymphovenous anastomosis in dogs led to its clinical application to bypass lymphatic obstruction in cases of lymphoedema, particularly following mastectomy. Three novel techniques to decompress obstructed limbs were investigated with the help of the John Mitchell Crouch Fellowship:

a) vascularised lymph node transfer,

b) omental grafting, and

c) systematic benzopyrones

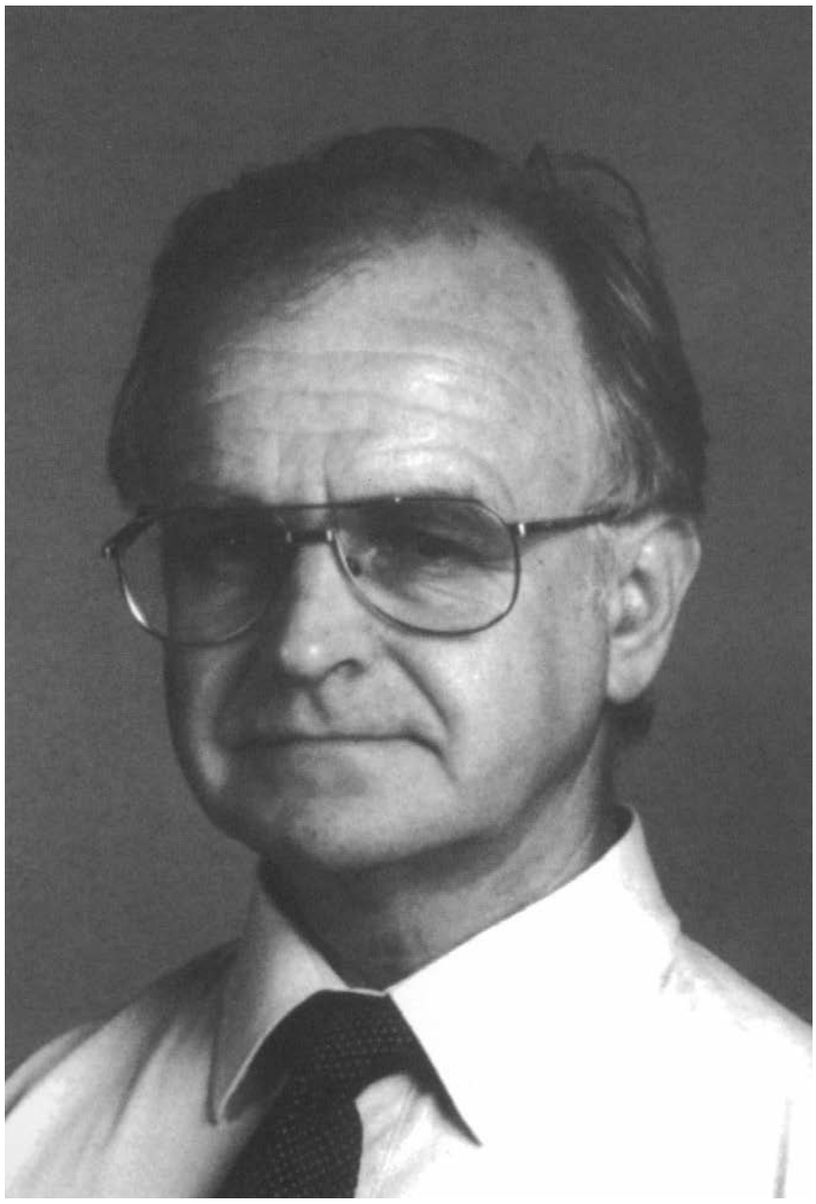
Methods (a) and (c) produced significant reduction in volume in lymphoedematous dog hind limbs.

5. Free jejunal grafts

Jejunal transfers in the dog were studied for oropharyngeal reconstruction and the efficacy of pH monitoring for flap viability as well as the long term effects on the graft or irradiation.

Benefits

These studies resulted in multiple publications and an MS and PhD thesis. They have enabled preliminary data to be obtained sufficient to attract subsequent NH&MRC grants for projects related to avulsion injury and tissue ischaemia. These has been direct application of the experimental findings into clinical practice.



1987

William Ben Runciman

Professor and Head, Department of Anaesthesia and Intensive Care
Royal Adelaide Hospital

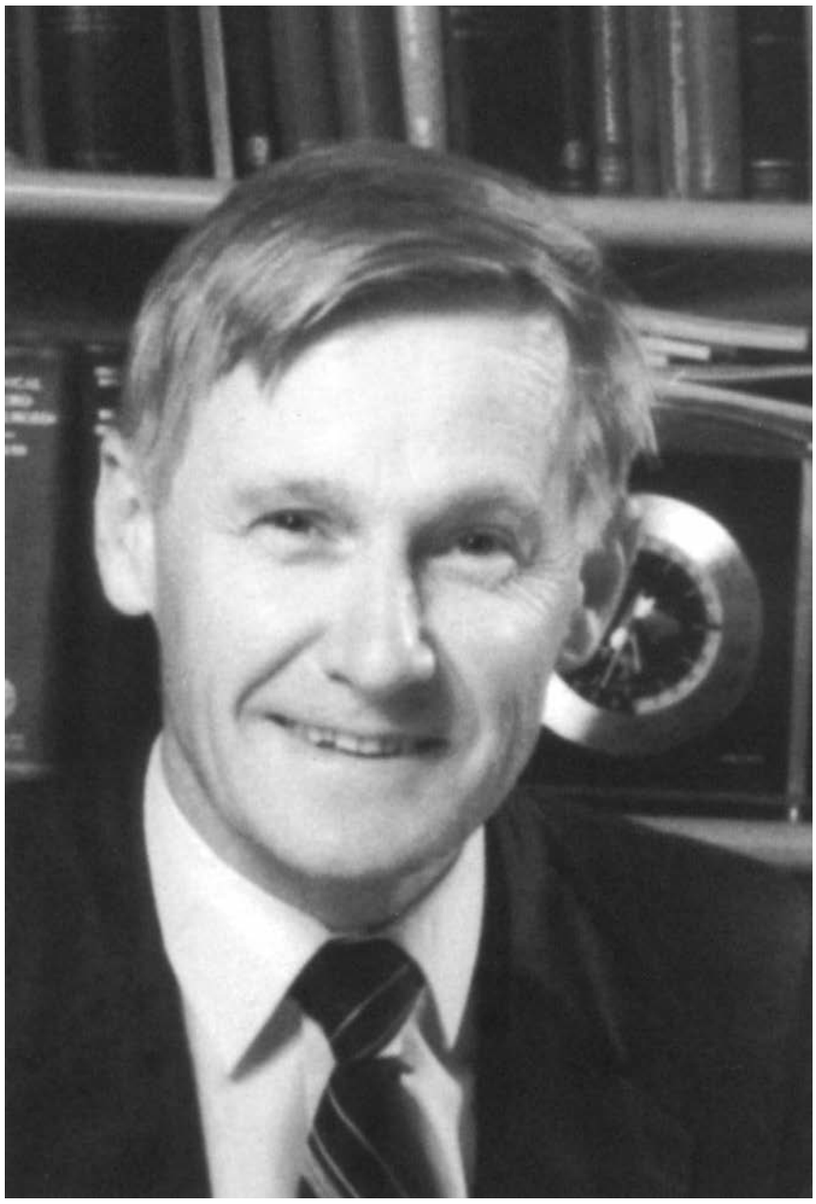
William Ben Runciman accepted the Foundation Chair of Anaesthesia and Intensive Care of the University of Adelaide in March 1988. The John Mitchell Crouch Fellowship funds were of crucial value in providing some initial laboratory equipment and infrastructure to allow the pilot studies to be undertaken which are now necessary for successful grant applications to national research funding bodies.

The funds were used to conduct initial studies into the toxicity of carbon monoxide. This is the commonest lethal poison in both developed and third world countries, and it has only recently been recognised that our understanding of its mechanisms of toxicity is seriously flawed. These pilot studies resulted in a successful three year NH&MRC grant, which was then followed by funds from Worksafe Australia. Some exciting work is still proceeding which is casting new light on how this important poison causes damage.

Funds were also used to conduct studies into measuring and concentrations of anaesthetic agents in the brain, heart and other important organs, and correlating these with effects. These paved the way for a two-year University of Adelaide Major Research Grant, which has recently been followed by an NH&MRC grant from 1993-95.

The John Mitchell Crouch Fellowship Funds were also used to correlate the concentrations of anti-arrythmic drugs in the myocardium with their effects both on the heart and on the circulation. These studies have now been followed by two successful National Heart Foundation grants.

The importance of being able to apply un-earmarked funds to basic infrastructure when starting a laboratory "from scratch" cannot be overestimated. The laboratory in the new academic Department of Anaesthesia and Intensive Care of the University of Adelaide has now attracted well over two million dollars in external funding over the last five years and is well funded for the next triennium; without the foundation provided by the John Mitchell Crouch Fellowship this would not have been possible.



1988

Ian Jeffrey Constable

Professor of Ophthalmology, University of Western Australia
Director, Lions Eye Institute
Head of Department of Ophthalmology, Sir Charles Gairdner Hospital

The John Mitchell Crouch Fellowship enabled Professor Constable to establish a biomaterials laboratory able to produce novel biopolymers for surgical implantation and to test these materials in tissue culture systems as well as experimental animals prior to human trials. The Fellowship was used to evaluate hydroxyethyl methacrylate (poly(HEMA)) as intraocular lens material following cataract surgery. Poly(HEMA) was found to be well tolerated as an intraocular lens material and has since been used in clinical trials on tens of thousands of patients worldwide. In fact, it is so well tolerated by tissues that minimal scar tissue reaction occurs and fibroblasts do not readily stick to it. For this reason, there is a risk that the material will dislocate into the posterior segment of the eye and further improvements were therefore required.

The Fellowship enabled the exploration of a variety of copolymers using poly(HEMA) with other materials. One particular copolymer consisting of poly(HEMA) and ethyl methacrylate was found to have superior qualities including more tensile strength and less fragility whilst still being able to be folded. Folding allows insertion through a tiny incision if the elasticity is present, allowing the shape to reform inside the eye.

During the term of the Fellowship non-toxic molecules were also developed which will absorb ultraviolet light for incorporation in hydrophilic polymers. Ultraviolet light toxicity following cataract extraction is of long-term concern as the normal lens and particularly the cataractous lens absorbs this part of the light spectrum.

The support of the John Mitchell Crouch Fellowship has allowed Professor Constable's research team to progress since that time to develop an artificial cornea, now undergoing extensive animal studies and to develop an artificial vitreous for possible use in surgery of the posterior segment of the eye.

1989

John Medwyn Hutson

Deputy Chairman and Director of the Surgical Research Unit
Department of General Surgery
Royal Children's Hospital, Melbourne

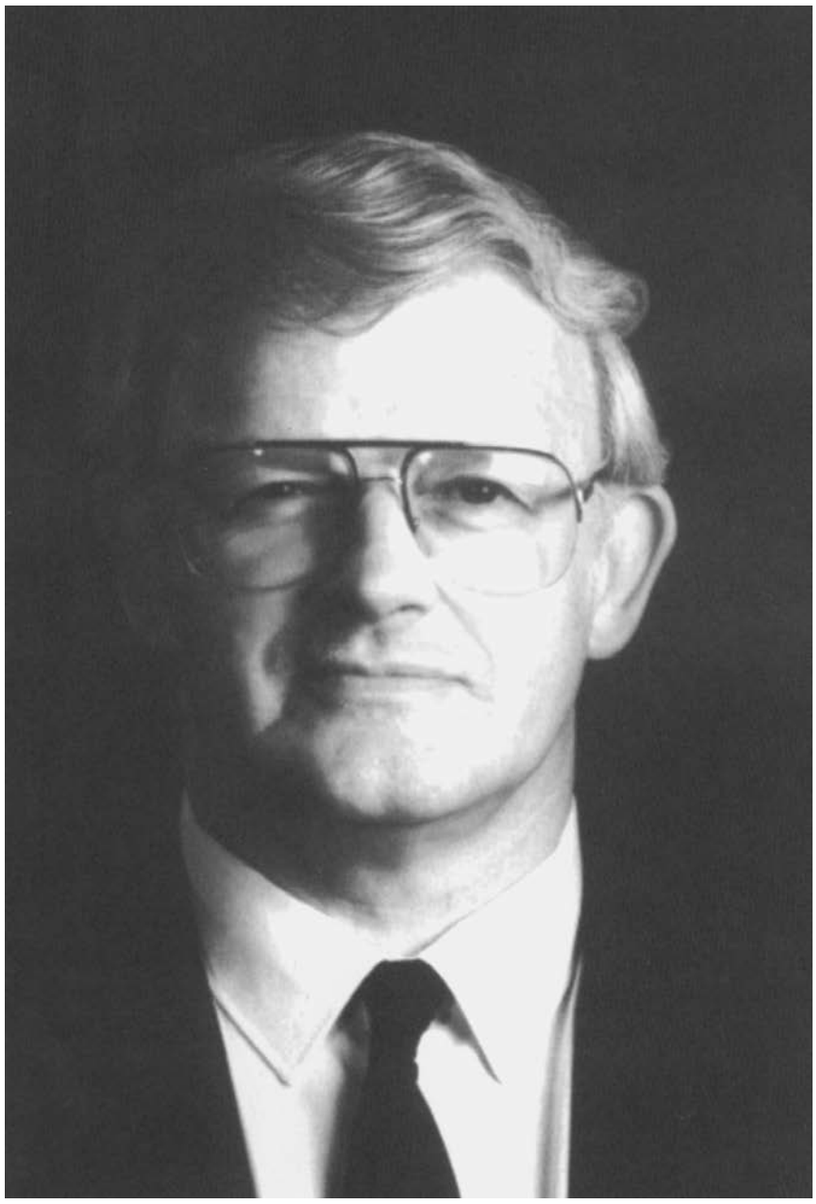
The 1989 John Mitchell Crouch Fellowship was applied to research into sexual development and testicular descent. Testicular descent is a hormonal mediated aspect of sexual differentiation which is important for paediatric surgeons because it is often abnormal. In the year of the Fellowship the hypothesis tested was that the genitofemoral nerve may mediate hormonal control of testicular descent, rather than testicular hormones acting directly on the gubernaculum, the structure described by John Hunter and believed to be responsible for migration to the scrotum. A major morphological study of the genitofemoral nerve was carried out and it was shown that it is larger in the male. In addition, it was shown that the gubernaculum initially ends in the groin and migrates to the scrotum. It is suggested this migration is controlled by the genitofemoral nerve.

Following the Fellowship year, investigation continued into various neurotransmitters found in the genitofemoral nerve to see if they might mediate the action of androgens on gubernacular migration. A large amount of evidence has been found to suggest that calcitonin gene-related peptide, a newly described neurotransmitter, may be responsible for gubernacular migration and testicular descent.

Recently, it has been found that the gubernaculum responds to CGRP both in organ culture and in vivo in a manner which suggests that it can replace the effect of androgens and the genitofemoral nerve. Although the work is not yet finished, it suggests now very strongly that androgens cause testicular descent by an indirect mechanism with release of CGRP from the genitofemoral nerve being the final common pathway.

This work holds some promise that CGRP may be used clinically to treat undescended testes in infants by stimulating gubernacular migration to the scrotum artificially. When the effect of CGRP on the gubernaculum was appreciated in 1991 a parent application for its potential clinical use as a treatment for undescended testes was taken out. Since that time, a large body of evidence has been accumulated to support this idea, that CGRP may be a final common pathway for controlling gubernacular migration and might indeed be useful as a treatment for infants with undescended testes.

This hypothesis has been incredibly controversial with many workers in the field remaining quite sceptical because of its novelty. Nevertheless, the evidence is accumulating at a rapid rate that it is likely to play a key role in testicular descent. Following the application for an international patent, funding support from AMRAD Corporation as been obtained, to determine whether the idea has any clinical usefulness to treat undescended testes.



1990

Geoffrey Ian Taylor

Head, Reconstructive Plastic and Maxillofacial Surgery Unit,
Royal Melbourne Hospital
Head, Plastic Surgery Unit at Preston and Northcote Community Hospital

The Background

Prior to the award of the John Mitchell Crouch Fellowship Mr Taylor had been involved, for nearly two decades, in anatomical studies of the blood supply of various tissues of the human body as the basis for microsurgical free flap transfers. This led to the one stage transfer of a skin flap in 1973. This was followed by living bone, living nerve and living tendon grafts, as well as various combinations of these, for reconstructive purposes.

In 1986 it was decided that the studies of the arteries would be expanded to encompass the entire body. This led to the ANGIOSOME concept of the body being constructed anatomically of 3 dimensional arterial territories which span between skin and bone. These territories are fed by named segmental or distributing arteries, they fit together like the pieces of an intricate jigsaw puzzle and they are linked by anastomotic arteries which are usually of reduced calibre. The picture, however, was incomplete and the John Mitchell Crouch Fellowship was awarded to study "the return journey" – the venous network of the body.

The Research

The study involved total body perfusion of the venous system in fresh cadavers with a radioopaque preservative mixture which included lead oxide and gelatin. The skin and subcutaneous tissues were removed as two halves, radiographed and a montage of the skin of the entire body constructed. Each vein was then dissected and the site and orientation of the valves were mapped on a tracing of the radiograph.

The deep tissues were examined in the same way, dissecting the deep veins in the intermuscular spaces. The individual muscles were studied next, by dissection and by X-ray, followed by the major nerve trunks in the upper and lower limbs. Finally cross sectional studies were performed to link the superficial and deep venous systems, thus completing the picture.

The investigation was completed in six subjects in the Department of Anatomy at the University of Melbourne. It spanned two years and involved four research workers. The results were correlated and compared with the research team's previous studies of the arterial territories. It was found that the body could be subdivided into venous territories – the VENOSOMES – which matched the arterial territories. Where reduced calibre "choke" anastomotic arteries linked the arterial territories they were partnered by avalvular bidirectional veins which linked the venous territories.

The Benefit

Apart from providing new anatomical data about the venous drainage of the skin, the muscles and the nerves, there have been several clinical applications. The information has added precision to the design of skin, muscle and nerve flaps; it has provided insight into the delay phenomenon, the pathogenesis of flap necrosis, varicose veins and venous ulceration as well as providing further information relative to the physiological process of the "muscle pump".

There have been several awards and recognitions. The work won First Prize in the essay contest of The Educational Foundation of the American Society of Plastic and Reconstructive Surgeons. It was published as the lead article in the Journal of that Society. Finally, three researchers, including Mr Taylor, have submitted successful M.D. theses based on this work.

1991

Andrew Henry Kaye

Professor of Neurosurgery,
Royal Melbourne Hospital and Melbourne University
Director of Neurosurgery and the Clinical Neuroscience Centre,
Royal Melbourne Hospital

There is no effective treatment for cerebral glioma, the commonest form of brain cancer. Photodynamic therapy (PDT) is a binary treatment modality, depending on the selective uptake of a photosensitizing compound by malignant tissue, followed by treatment with light of an appropriate wavelength to activate the sensitizer and cause selective destruction of the tumour. Professor Kaye's studies have investigated the basic cellular mechanisms of PDT, including the uptake of photosensitizer into the tumour and the sub cellular localisation so that the therapy can be optimised. A colleague, Dr Hill has developed an assay in which the porphyrin sensitizer is extracted from the cells and the sub cellular organelles and measured flurometrically.

The assay has quantiated the uptake of haematoporphyrin derivative (HpD), the bench mark photosensitizer, into tumour and normal brain taken at surgery from patients treated by Professor Kaye at the Royal Melbourne Hospital.

These results show that HpD is selectively localised into all grades of glioma and there is a direct correlation between the grade of glioma and HpD levels in the tumour, with the highest grade glioma (glioblastoma multiform) having the highest porphyrin uptake, being 30 times that taken up into normal brain. The assay has also shown the sensitizer is selectively localised into lower grade tumours (8 to 10 times) indicating the treatment may be of use in these otherwise often untreatable cancers).

These studies have demonstrated that photodynamic therapy will cause selective destruction of brian tumours within critical levels of sensitizer doses and light irridiation. Following therapy the cancer cells undergo a selective necrosis with the sparing of the adjacent normal brain. The sub cellular and intra tumour distribution of sensitizers has been determined using confocal laser scanning microscopy. The sensitizer HpD, which is comprised of monomeric and dimeric components localised in the cytoplasm of glioma cells, was not taken up by the nucleus.

However, within the cytoplasm distinct highly localised regions of fluorescence were present in the perinuclear region. Ultracentrifugation studies have shown this fluorescence is associated with the mitochondrial fraction of these cells. In contrast to HpD, which exhibits equal localisation to both the cytoplasm and mitochondria, a purified dimeric porphyrin was found to be associated with only the cytoplasm, whilst the purified monomer, BOPP was selectively localised to the mitochondria alone.

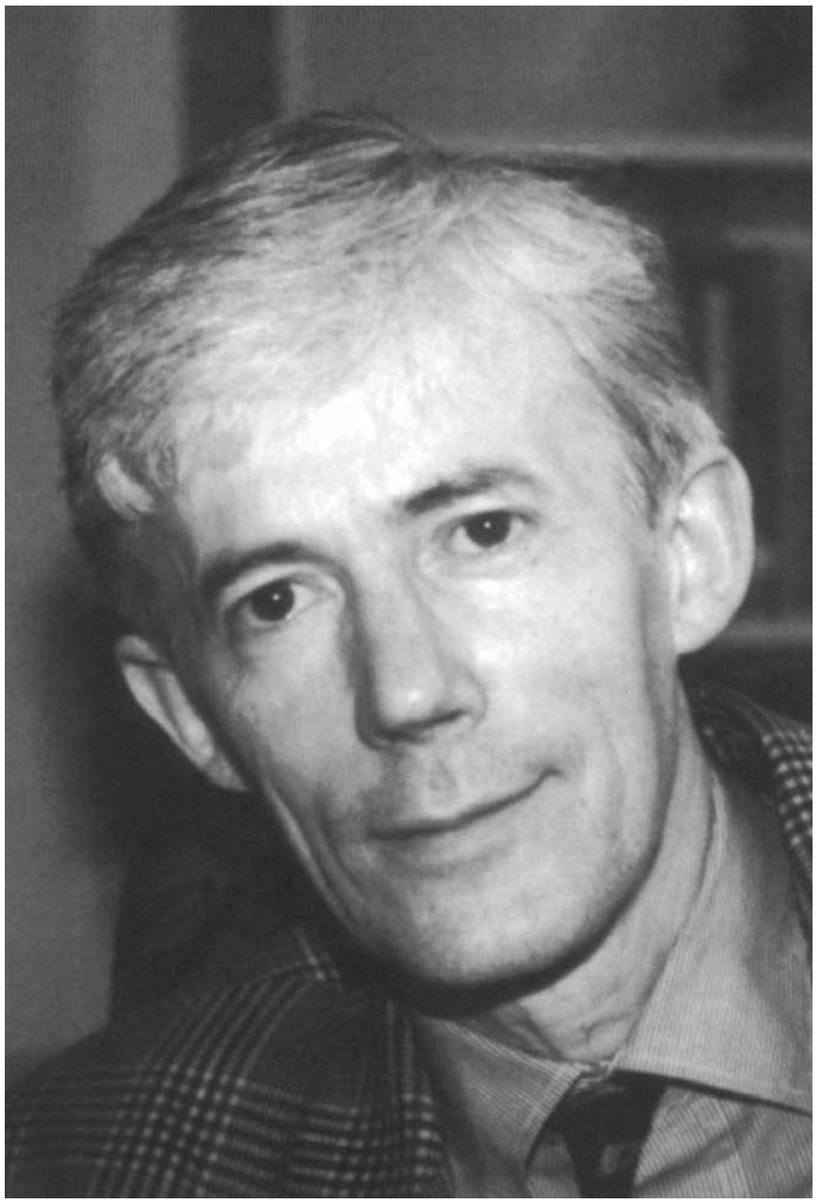
The basis for these differences is not known and is currently under investigation. Confocal laser scanning microscopy studies of other porphyrin molecules have also shown uptake into both mitochondria and lysosomes. Confocal laser scanning microscopy of tissue taken at operation has shown that HpD is present in the cancer cells infiltrating into the normal adjacent brain. It is these cells that are responsible for tumour recurrence after conventional therapy and the demonstration of sensitizer in these infiltrating cells is an essential prerequisite for the treatment to be effective clinically.

The pharmacokinetics and photosensitizing properties of boronated porphyrins synthesised by Dr Steven Kahl of the University of California, San Francisco have been determined in Professor Kaye's laboratory. Studies have shown a highly selective uptake of these compounds (400 times compared with normal brain) and an active photosensitizing property. Studies with confocal laser scanning microscopy have demonstrated the sensitizer to be localised in discrete organelles in the perinuclear region, which have been shown to be mitochondria.

Further studies will be undertaken to assess the possibility of combining photodynamic therapy with boron neutron capture therapy as combined adjuvant treatments for cerebral tumours.

Professor Kaye has used photodynamic therapy as an adjuvant treatment in 102 patients with cerebral tumours at the Royal Melbourne Hospital. The initial results are encouraging and the therapy does appear to have a clinically beneficial effect. The median survival time of patients with glioblastoma multiforme (the most malignant type of cerebral glioma) treated with surgery, photodynamic therapy and radiotherapy is twenty three months, compared with historical median survival of seven months in a matched series. 11 patients have lived longer than two years.

Studies are continuing to improve the effectiveness of photodynamic therapy by optimising sensitizer properties, its delivery and light dosimetry.



1992

Wayne Allan John Morrison

Hugh Devine Professor and Head, Department of Surgery,
University of Melbourne and St Vincent's Hospital, Melbourne
Deputy Director, Microsurgery Research Centre,
St Vincent's Hospital, Melbourne

The research program at the Microsurgery Research Centre, St Vincent's Hospital, is predominantly reconstructive plastic surgery and microsurgery but it crosses many disciplines including basic science. Although there is input to each project from multiple researchers, Professor Morrison's specific areas of interest during the year of the John Mitchell Crouch Fellowship were:

1. Angiogenesis in the production of prefabricated skin flaps

This concept involved the implantation of a vascular pedicle under an area of skin which is suitable in colour, texture,thickness etc. for a repair and subsequent transfer to a specific matching defect at another site. The pedicle induces angiogenesis which revascularises the overlying skin to an extent that will allow transfer of its vascular pedicle by microvascular anastomosis. The project was carried out in the thigh of a rabbit and various combinations of vascular implementation and flap sizes were investigated. At three months a vast new network of vessels had migrated into the overlying flap tissue sufficient to allow its safe transfer by microvascular anastomosis. This process hopefully can be streamlined by the use of angiogenic growth factors which are currently being investigated. It has direct clinical applications.

2. Venous flaps

In some circumstances skin flaps can survive based solely on a venous blood supply and these can be transferred by microvascular anastomosis. The advantages include multiple and more acceptable donor areas, thin skin and the preservation of arteries which would conventionally require sacrifice. The design of these flaps and the mechanism and pharmacological enhancement of their survival was investigated in dogs' legs based on varying configurations of the cephalic vein. Reliable survival was obtained if arterial blood was directed iso- or retrogradely through a flap containing a vein only, provided an independent venous drainage was included. Continuing studies using vital microscopy are being undertaken.

3. Vessel substitutes

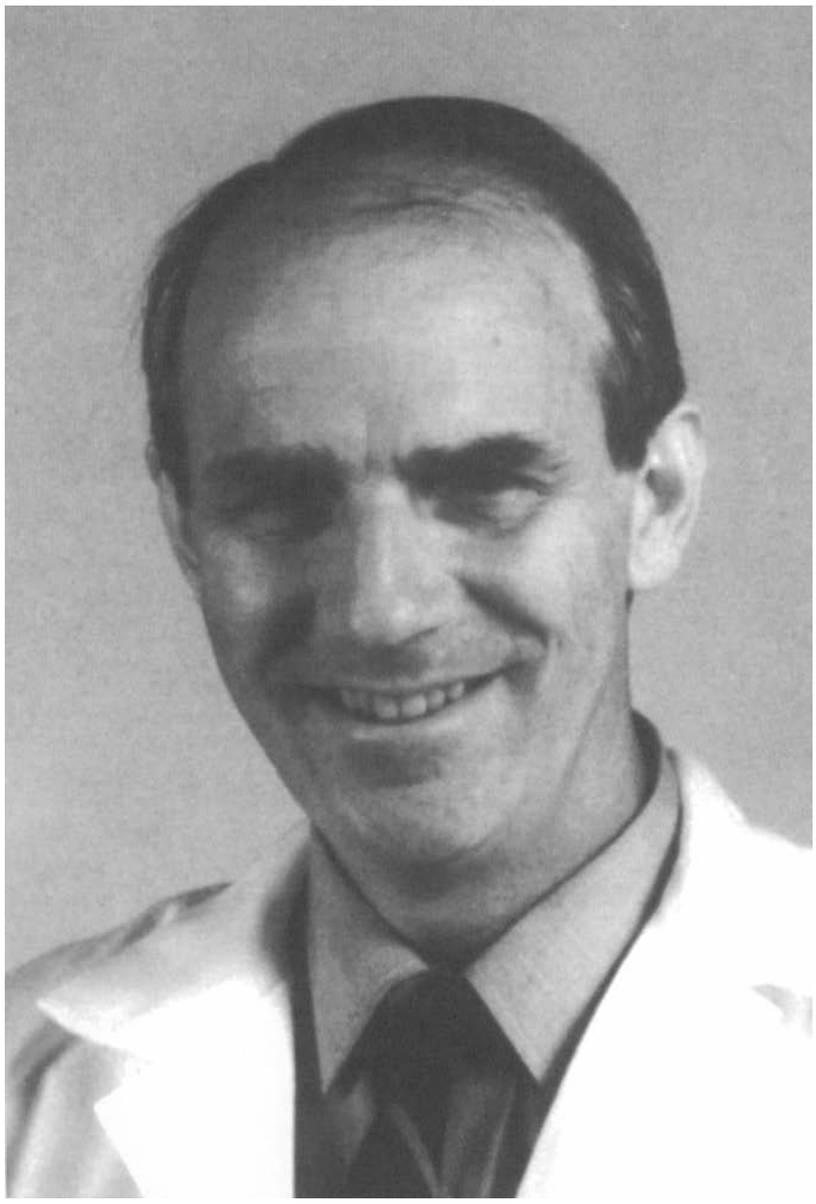
To date no long microvessel substitute has been successful in situations of low flow. Investigations in the rabbit have shown that microvascular grafts preserved at 4°C for periods of up to 10 weeks, when reinserted into the donor animal reliably remain patent for at least three weeks, long enough to allow independent survival of any transferred flap on such a vessel by vascular ingrowth from the surrounding tissues.

4. Epiphyseal transfer

The transfer by microvascular anastomosis of the distal ulnar epiphysis into the midshaft of a humerus in the dog demonstrated that the limb can be lengthened beyond normal expectations. This has potential clinical application in congenital and acquired limb deficiencies particularly in children.

Benefits

The prestigious John Mitchell Crouch Fellowship has benefited the recipient and particularly the Microsurgery Research Centre in many ways. It brings great kudos to the Centre, particularly so as two such Fellowships have been awarded to the Centre in recent times. Specifically it has benefit by partially funding the projects outlined above, two of which have subsequently been able to attract substantial NH&MRC grants. Several publications, an MS and a PhD thesis have been associated with these projects and they have led to direct clinical applications in the human.



1993

GLYN GARFIELD JAMIESON

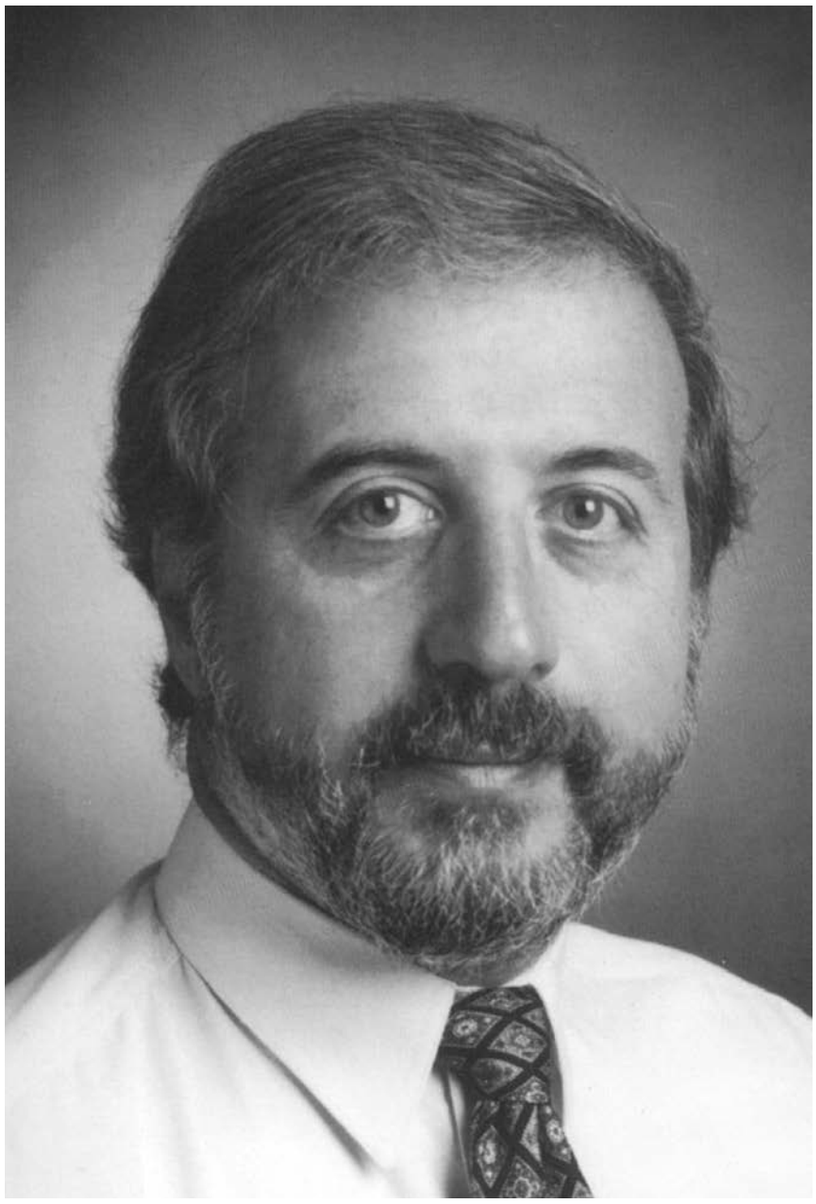
Professor of Surgery, Royal Adelaide Hospital

Throughout his surgical career, Professor Jamieson's research has been involved with physiological mechanisms and particularly with the application of those mechanisms to the clinical situation. Initially, this research was in the field of cardiovascular physiology, but beginning in the late 1970's and throughout the 1980's to the present the emphasis changed to upper gastrointestinal motility.

For the past seven years, the main scientific thrust of this research has involved the use of a pig model of gastric emptying. This has been used to examine the physiological mechanisms which cause gastric emptying and the disturbance of these mechanisms by operations. Both accepted operations and experimental procedures have also been studied. These studies have led to one publication in the Journal of Physiology and two publications in the American Journal of Physiology (and one further accepted for publication), as well as several other publications in the surgical literature.

Over the past three years, with the able assistance of De Mehran Anvari and Dr Charles Malbert, the program has led to some extremely interesting results which may alter the basic understanding of the way in which the stomach empties. The fundamental finding has been that the body of the stomach generates pulsatile waves which strip over the whole of the stomach, leading to emptying. These waves have previously been thought to be confined to the antrum. This work led to six abstracts being accepted for presentation at the American Gastroenterological Association Meeting in 1993.

These findings may have surgical relevance and it is in this regard that it is intended to continue studies in the animal model. It is possible to retain an innervated pylorus associated with various types of gastric resection, and by maintaining a muscle bridge between the retained part of the proximal stomach and the pylorus, it is hypothesized that relatively normal gastric emptying can be retained. Preliminary studies suggest that a functioning muscle bridge is not only technically possible, but does not aid regulated emptying from the stomach. Thus in situations such as refractory gastric ulcer, early gastric cancer and refractory duodenal ulcer, it may be possible to carry out either an antrectomy, a partial gasrectomy or a proximal gastric vagotomy and antrectomy, retaining an innervated pylorus and a muscle bridge assuring coordination of the pylorus with the proximal retained stomach.



1994

James Tooulli

Professor of Surgery
Gastrointestinal Surgical Unit, Department of Surgery
Flinders Medical Centre, Flinders University of South Australia

Background

The sphincter of Oddi is a small smooth muscle structure situated at the junction of the bile duct and pancreatic duct with the duodenum. When first described, Oddi postulated that abnormalities in its function might be associated with a number of clinical syndromes. However, it has not been until the 1980s with the development of sophisticated techniques for studying this small structure in man that we have conclusive evidence to support Oddi's original hypothesis.

Laboratory and clinical studies have defined to a large degree the normal physiological function of the sphincter of Oddi. In addition, the clinical studies have identified manometric abnormalities which then lead to naming the syndrome of sphincter of Oddi dysfunction. This clinical syndrome is quite uncommon but when diagnosed, has a female predominance and is unmasked following cholecystectomy.

Patients present with recurrent upper abdominal pain characteristic of a biliary aetiology. Often clinicians believe that these patients might have a recurrence of stones in their bile duct but relevant investigations often show no abnormalities. In some patients, the bile duct may be abnormally dilated and thus there is the suggestion that the problem might arise from the sphincter of Oddi.

These studies have demonstrated and defined the manometric criteria which help to identify patients with objective motility abnormalities of the sphincter of Oddi. Furthermore, they have identified the type of manometric abnormality which can be treated by endoscopic division of the sphincter and lead to a successful resolution of the symptoms.

Many of the studies that have been summarised above were conducted in the 1980s and primarily concentrated on the biliary aspect of sphincter of Oddi dysfunction. However, all along, a number of patients were being referred with idiopathic recurrent pancreatitis and these patients had also been subjected to manometric studies of their sphincter leading to the view that this entity might also be another syndrome associated with a dysfunctioning sphincter of Oddi.

The award of the John Mitchell Crouch Fellowship in 1994 provided the impetus to focus the research activities in the area of the pancreas and the association between the sphincter of Oddi and the production of pancreatitis.

Laboratory Investigations

The normal motility of the pancreatic component of the sphincter of Oddi had not been systematically investigated until the studies which were made possible by this award from the College. The laboratory had previously and continues to conduct extensive studies on the biliary component of the sphincter of Oddi. However, following the award of the Crouch Fellowship, studies were commenced on the normal physiology of the pancreatic component of the sphincter of Oddi and its relationship to the biliary component of the sphincter. The initial studies which recorded the motility of the two components of the sphincter both independently and simultaneously, revealed that the sphincter of Oddi is a little more complex than previously believed. The studies indicated that the sphincter in both the pancreatic and the biliary side has two areas of high pressure activity in both the proximal and distal ends. The motility of the two components of the sphincter i.e. biliary and pancreatic appears to be simultaneous and hence is coordinated. Experiments to this day have not shown stimuli which might selectively act on one versus the other sphincter component. However, a variety of intraluminal stimuli have not as yet been evaluated.

Following these initial studies, it was important to see whether a pancreatitis model could be developed in order to evaluate the relationship between sphincter of Oddi motility and pancreatitis. This model has been successfully developed with studies that have been conducted subsequent to the year of the award of the Fellowship.

For the continuation of these studies, NH&MRC funding has been secured and undoubtedly the initial studies that were conducted under the auspices of the Fellowship, assisted in the success of obtaining the funding.

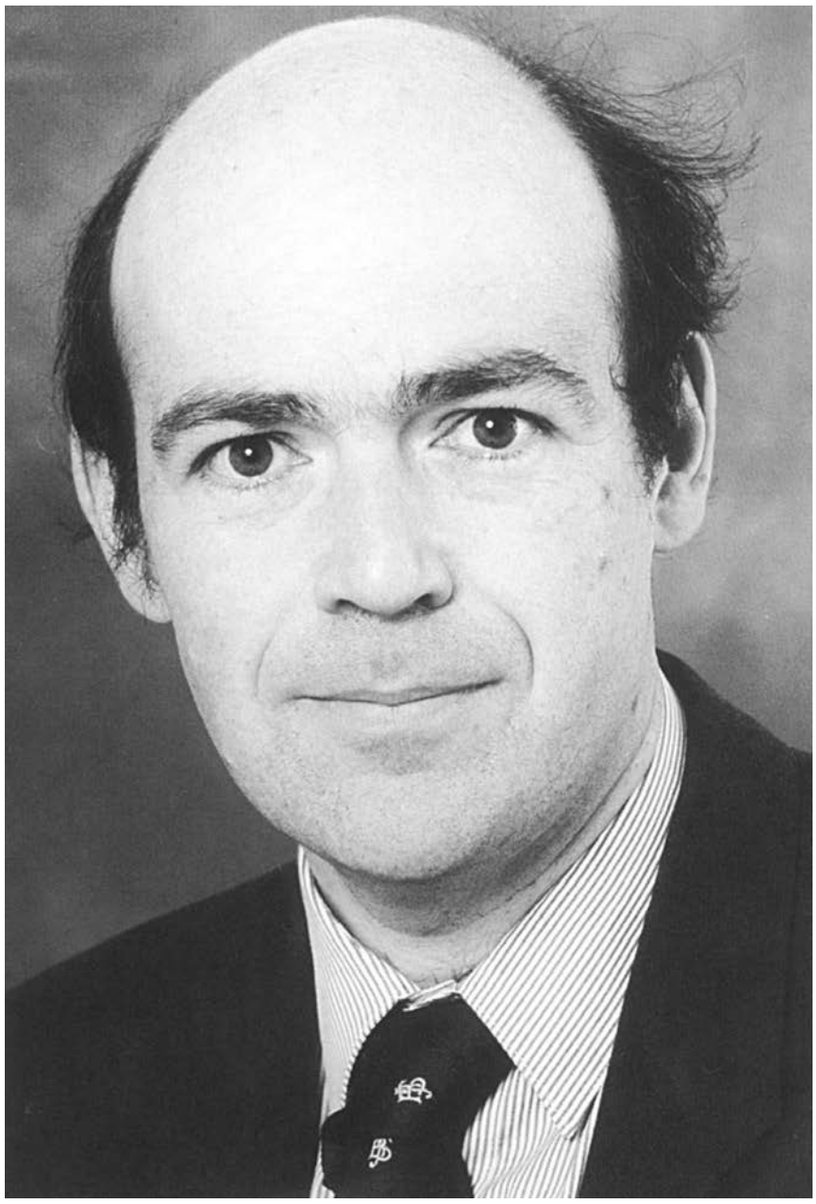
Clinical Investigations

At the same time of the conduct of the laboratory investigations described above, it was decided to evaluate the outcome of treatment of those patients who had presented with idiopathic recurrent pancreatitis. This time had coincided with a 10 year experience in treating 35 patients who presented with idiopathic recurrent pancreatitis and who had been followed for a median of 2 years. Prospective data had been maintained on all of these patients and thus accurate data was available for analysis during 1994. The analysis showed that patients who presented with idiopathic recurrent pancreatitis and who had demonstrated on sphincter of Oddi manometry a stenosis of the pancreatic sphincter, responded well to treatment. The treatment that had been offered was an operative sphincteroplasty and septoplasty which in essence, opened both the pancreatic and the biliary components of the sphincters, thus allowing free drainage of bile and pancreatic juice into the duodenum. On the 2 year follow up, 85% of the patients who had a stenosis of the sphincter and had been treated as indicated above were either totally cured or significantly improved so that they now only experienced occasional mild abdominal

symptoms. None of the 85% of patients had had recurrent episodes of pancreatitis requiring hospital therapy. These results were significant in their findings and have provided firm guidelines for the management of these difficult patients.

Conclusion

The award of the John Mitchell Crouch Fellowship was significant in that it allowed a change in direction and focus of the research that was being conducted since the early 1980s. As a result of these findings, there are now strongly supported recommendations for the investigation and treatment of patients with idiopathic recurrent pancreatitis. In addition, there is now an active research programme which is evaluating the role of the sphincter of Oddi in the production of pancreatitis. It is postulated that the sphincter may be involved in not only the production of idiopathic recurrent pancreatitis but also in the much commoner condition of biliary pancreatitis. It is hoped that the outcome of this new focus of the research activity will be of assistance in the management of these patients.



1995

DAVID LAWSON MORRIS

Professor and Head of the University of New South Wales Department of Surgery
The St George Hospital, Sydney

The quest for the non-cytotoxic control of GI cancers is gathering some momentum! Our contribution to this research so generally supported by this Fellowship in the last year has included:

Histamine

We reported several years ago that some human colorectal cancers have functional histamine receptors. We also demonstrated that tumour infiltrating lymphocyte (TIL) is significantly improved by cimetidine in patients with colorectal cancer (CRC), probably by directly blocking the effects of histamine on lymphocyte function. We have just completed a randomised study in breast cancer and are well advanced with a dose finding study in colorectal cancer. We have studied the phenotype of TIL in colorectal cancer patients and started functional studies of TIL in control/cimetidine patients. We have reported histamine concentrations in both human breast and colorectal cancer which are sufficient to inhibit lymphocyte function and in breast cancer are highly significantly different from normal breast. We have also reported synergistic activity of 5-FU and cimetidine in in vitro culture and sorting out the importance of these three effects of cimetidine on cancer: direct growth factor antagonism.

Vitamin D_3 analogue

We have in the last year reported potent inhibitory activity of a vitamin D3 analogue against 6 of 8 human colorectal cancer cell lines tested, and have successfully inhibited growth of xenografts. We have recently shown that vitamin D3 receptor status measured by PCR predicts sensitivity to treatment. Current work includes testing the effects of the compound on advanced and metastatic disease, as well as dosimetry studies. We believe this compound will be used in man in the near future.

Gastrin

The ability to predict which cancers will respond to a potent gastrin receptor antagonist has been measured by the assay of gastrin precursors. It seems likely that incompletely processed gastrin is functionally important and is a prime target for manipulation.

There are other important non-cytotoxic approaches to GI cancer being actively pursued by other groups and several other projects planned in our group. Whilst much work remains to be done, it seems likely that Goliath will fall. Our ability to treat advanced or metastatic GI cancer is very limited. I am grateful to the John Mitchell Crouch Fellowship for the support of our research at this exciting time.

1996

JOHN CHARLES HALL

Associate Professor of Surgery,
The University of Western Australia.

Professor Hall's interest in surgical nutrition took root in the late 1970s when he was working as a research fellow in Leeds with Professor Geoffrey Giles. Nutrition was a very topical issue for surgeons at that time because of the introduction of nutritional support techniques that allowed patients to be fed intravenously (parenteral nutrition).

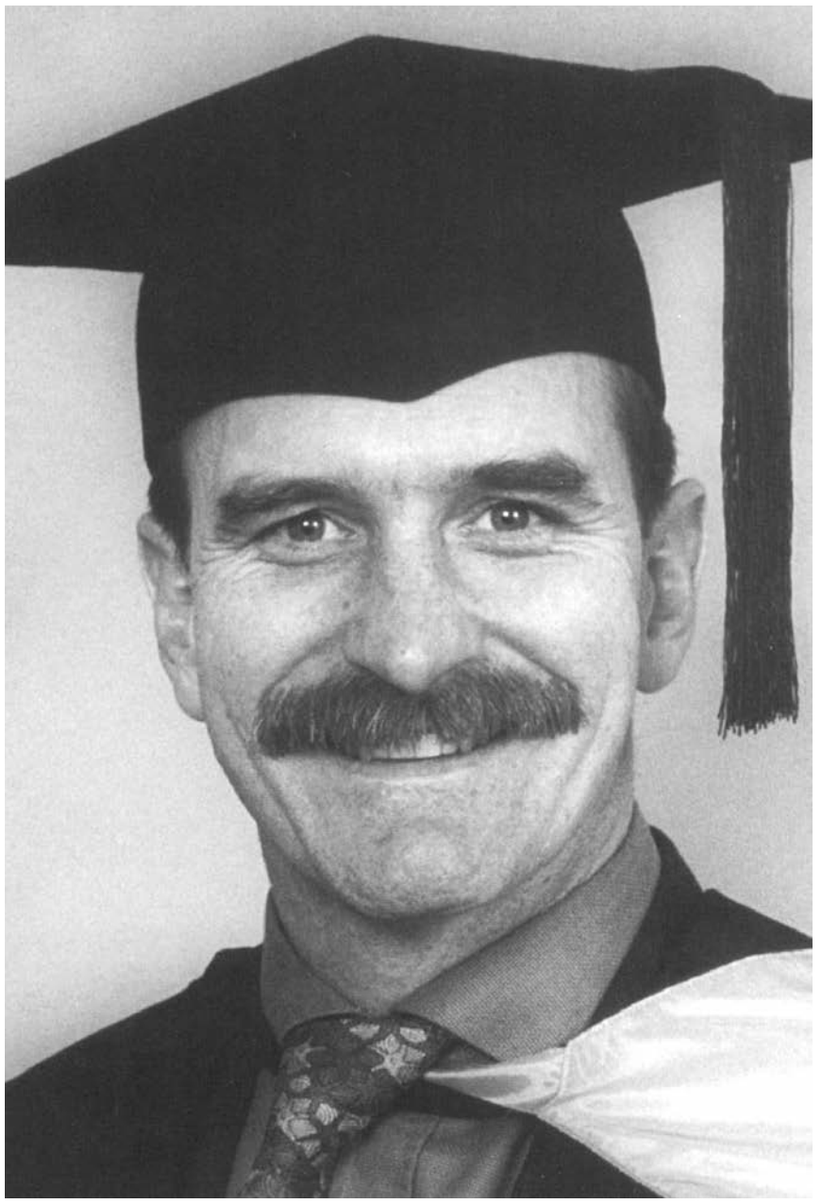
The initial hope was that nutritional assessment techniques would identify a group of surgical patients who were undernourished and would benefit from aggressive parenteral nutrition. However, such 'skeleton in the closet' theories failed to appreciate the complexity of the underlying biological events, particularly those relating to sepsis in critically ill patients. When it became apparent that assessments of nutrition status had limited utility, attention was directed towards mechanisms within specific organ systems.

An area of specific interest was the effect of undernutrition on the gastrointestinal tract. The gut contains a labile pool of proteins that are utilized by other tissues during periods of catabolic stress. Starvation results in atrophy of the gut and this process is not reversed by the provision of conventional parenteral nutrients. The most obvious reason for this phenomenon is a lack of trophic factors stimulated by the presence of food. However, small bowel that has already been defunctioned undergoes further atrophy during parenteral nutrition. Such atrophy of the gut may contribute to a number of adverse clinical events, the most obvious being a delayed adaptation of the remaining intestine after extensive resectional surgery.

Attention was then directed towards the role of glutamine as a conditionally-essential gut nutrient. The intestine is a major site of glutamine metabolism and utilizes this amino acid as its primary respiratory fuel. However, conventional solutions of parenteral nutrients do not contain glutamine because it is unstable and degrades to form toxins.

A dose-response study using laboratory animals demonstrated a strong relationship between the concentration of parenteral glutamine and the extent of gut atrophy. A desire to evaluate the functional problems associated with gut atrophy has led to experiments evaluating the permeability of the bowel and the passage of microbes across the wall of the gut i.e., microbial translocation. There is now accumulating evidence which suggests that such deficiencies in the barrier function of the gut play a key role in the development of the multiple organ failure syndrome in critically ill patients.

Professor Hall has used the John Mitchell Crouch Fellowship to commence a clinical trial evaluating enteral glutamine within the Intensive Care Unit at Royal Perth Hospital. The results of this clinical trial will have considerable significance for all critically ill patients who require nutritional support.



1997

PADDY DEWAN

Associate Professor of Paediatric Surgery
Royal Children's Hospital, Melbourne

The main project will involve the development of a model of vesicoureteric reflux in fetal pigs. The sows will be operated on in mid-gestation and the fetuses will have one of their ureteric tunnels ablated. The fetuses will then be allowed to go to term and the effect on the kidney will be assessed and compared with the normal contralateral side. At present it is thought that the kidneys are malformed as part of the embryopathy of the renal tract; recent human prenatal diagnosis studies have suggested the kidneys may be damaged by vesicoureteric reflux in utero. This fetal pig research will hopefully help identify if the vesicoureteric reflux alone causes injury to the kidney, information which will impact on the prenatal and post-natal management of a disease which affects 2% of the population.

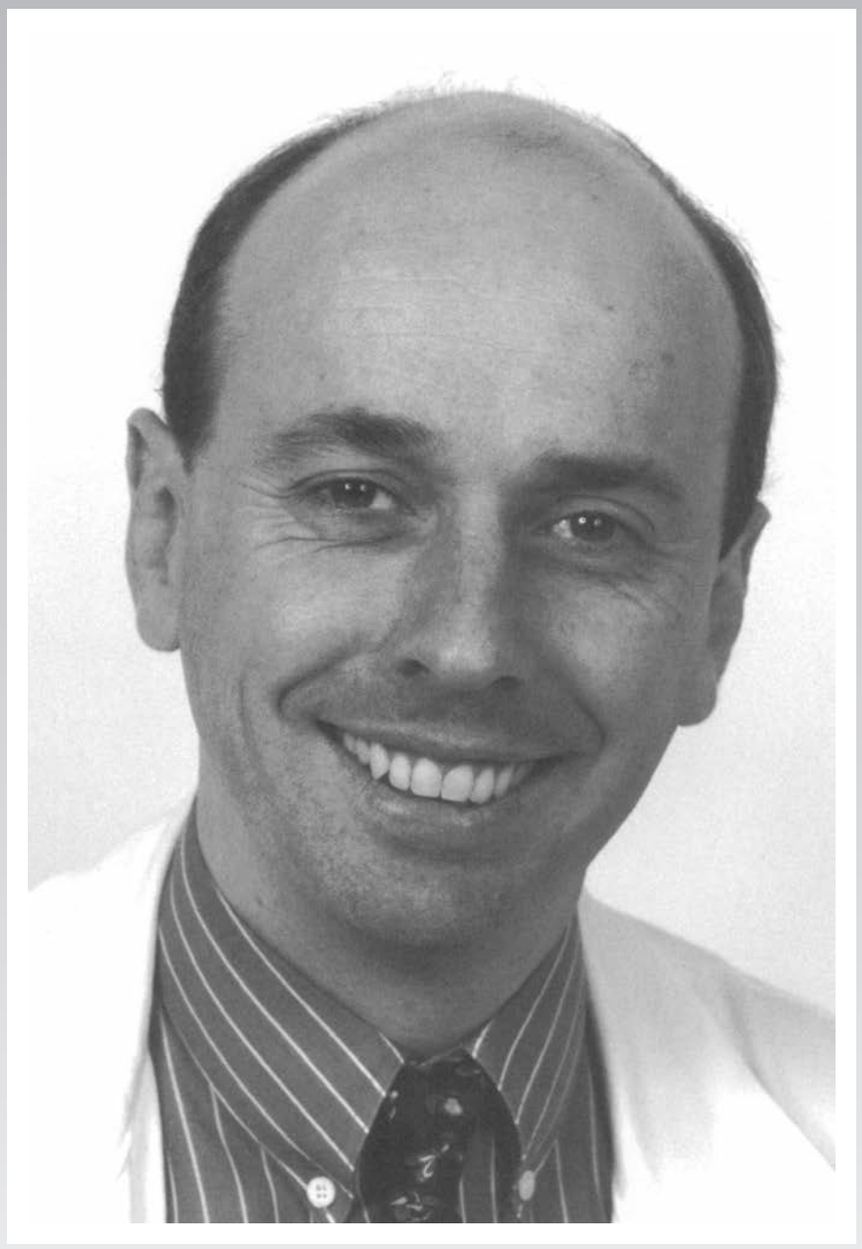
An associated project will look at a model of urachal obstruction in the male fetal sheep. It has been known that obstruction of the urethra in the male fetal sheep causes nephropathy, only when the urachus is obstructed. The finding that the upper tract changes will occur if only the urachus is obstructed is a recent finding from the laboratory of the Boston Children's Hospital. A study is planned in which the urachus of 10 male sheep fetuses will be obstructed in mid-gestation, following which changes in the bladder, ureters and renal parenchyma will be assessed at birth. The changes seen may account for those boys who present with high grade vesicoureteric reflux in the neonatal period without any evidence of urethral obstruction.

A library of urethral endoscopic images is to be established for all such procedures conducted by the Urology unit at the Royal Children's Hospital. This will involve the video storage of the urethral images, patient demographic data and diagnoses on computer which will allow retrieval and correlation of the findings.

The second major project relates to the further development of bladder augmentation model. We have previous experience in bladder augmentation in a sheep model in which the bladder mucosa has been reinforced with stomach, colon, omentum and peritoneum. This current study, with several important refinements, will follow previous research plans which have proved to be very successful. Ten, six month old, male sheep will have be anaesthetised with thiopentone, halothane and nitrous oxide. The abdomen will be opened through a lower midline incision, a double lumen catheter inserted into the bladder and a urodynamic study will be performed. The fourth stomach will be delivered and a length of the greater curve will be mobilised as a vascularised flap on the right

gastro-epiploic vessels, having divided the proximal branches. After preparing the vessels, the isolated segment will be clamped and incised and the remainder of the stomach will be closed. The gastric mucosa of the isolated segment will be carefully dissected from its muscle by diathermy, ensuring complete removal of the epithelium, muscularis mucosa and most of the submucosa. Samples of the resected mucosa and submucosa and the resulting demucosalised gastric muscle will be examined histologically. The bladder will then be prepared in the autoaugmentation manner (as extensively used in other components of the units research program), by removing the detrusor from the urothelium, without opening the bladder lining. A second urodynamic study will then be carried out to examine the effect of detrusor removal on the bladder and the bladder outlet resistance. The demucosalised gastric flap will be sutured to the free edge of the bladder muscle, thus covering the denuded outer surface of the urothelium. The abdominal incision will be closed in layers. A catheter will be left in place for 10 days ensuring continuous bladder drainage. A cystogram will be performed at 10 days, with the sheep awake, to ensure there is no bladder leak. The catheter will be removed and the animal will be returned to the farm when recovered from the surgery and feeding well. A third urodynamic study will be carried out six month post-operation when the animals are 12 months old. The bladder will be catheterised with a double lumen suprapubic catheter under ultrasound guidance. Following urodynamics, the animal will be sacrificed with a lethal dose of barbiturate and the bladder harvested for histological examination. For all urodynamic studies, the bladder will be filled with normal saline at a rate of 30 ml per minute, the volume/pressure profile will be recorded on purpose built software, and a hard copy obtained. The volume and pressure at leak point and three quarters capacity and the volume at a pressure of 20 ml/cmH2O will be determined. The compliance at any point of the study is defined as volume/pressure (ml/cm H2O). Five six month old male sheep will be anaesthetised as above. The abdomen will be opened through a lower midline incision, a double lumen catheter inserted into the bladder and a urodynamic study performed as described. The incision will then be closed in layers. A catheter will be left in situ for 10 days as for the AAGC group and a cystogram performed with the sheep awake. The animals will go to the farm and return at 12 months of age for urodynamics and sacrifice as above. Thus, this group of sheep will have undergone similar procedures to the AAGC group except for the actual augmentation surgery. This will allow determination of factors related to the augmentation alone, which influence the outcome of the procedure. Five twelve month old male sheep will undergo no operative procedure other than the insertion of a suprapubic double lumen catheter and urodynamics. The animal will then be sacrificed. The data for this group will be added to limited data available for 12 month old sheep from previous studies. In addition, data is available for a large number of six month old normal controls. The parameters obtained for the AAGC and sham controls will be compared with these normal controls.

The above work will be supported by the employment of a graduate research Veterinary student and a Paediatric Surgical research fellow. The Fetal pig project will also be assisted by funds from a Channel 7 research grant.



1998

Guy John Maddern

Director of Surgery, Queen Elizabeth Hospital
RP Jepson Professor of Surgery, University of Adelaide

The electrolytic ablation of liver tumours has been the major area of ongoing work during the twelve months of the John Mitchell Crouch Fellowship. Extensive experimental work has been performed looking at the effect of multiple electrodes applied to liver substance. By using multiple electrodes it is possible to create a much more rapid lesion and therefore destroy more tumour in a short period of time. This has substantial clinical relevance as it enables the operation and the anaesthetic for the management of patients with multiple metastatic deposits to be shorter.

Following on from this work with multiple electrodes we have also performed extensive animal work looking at the effect of occluding the hepatic inflow to the liver during the time of the electrolytic treatment. This so-called "Pringle manoeuvre' has been associated with an almost doubling of the rate at which the lesion is created. There are significant clinical implications for this as it may enable an even more rapid development of a therapeutic lesion to occur. Unfortunately, in a number of the pigs studied there were deaths associated with this manoeuvre. It is not yet clear whether this is due to an overburden of toxins being created by the lesion or whether, in fact, pigs are less resilient to the Pringle manoeuvre. Attention has also been focused on the development of percutaneous techniques to insert the electrodes without the necessity of a major laparotomy. We have been working closely with not only the electrode manufacturers but also Cook Australia to try and develop an appropriate system. It appears that we may now have an ultrasonic reflective needle which we can place in the correct position within the lesion and down the needle it is possible to introduce the electrode cable. We have now successfully performed this approach in the open operation and are planning to begin animal and subsequently human studies in the near future.

Another important aspect of this work has been to commence a randomised controlled trial looking at patients who are undergoing ablative electrolytic treatment compared with a control group in which conventional treatment of chemotherapy or no treatment is offered. The early results are extremely pleasing with all patients showing response from the electrolytic treatment. Three patients have shown complete resolution of lesions, one has had to have a second treatment for a recurrent lesion which was large and awkwardly positioned. The technique may be of enormous value to these patients who would otherwise be inoperable. We have used the basis of this work to make an application for an NH&MRC grant in the year 2000.

From this work a number of publications have emerged or are in the process of being reviewed and it is expected that in excess of ten publications will arise from the work of the last twelve months describing our animal and patient experience with this technique. It was also possible to present some of this early work to the Royal Australasian College of Surgeons Annual Scientific Meeting in Auckland this year as the Foundation Visitor for the General Surgery section of the College.

1999

David Charles Gotley

Professor of Surgery, University of Queensland

Cancer research has traditionally focussed principally on the properties of the tumour cell as the drivers of tumour growth, invasion and metastasis, with the host organ playing the role of a passive recipient. Recently, the role of normal host stromal cells in these processes has been recognised, and it is now clear that the outcome of tumorigenesis depends as much on interactions between tumour and host cells, as on intrinsic properties of the tumour cells themselves. This paradigm is not new, since it was enunciated in Stephen Paget's "seed and soil" hypothesis well over 100 years ago and the principal is apparent to any clinician that deals with patients with malignancy. The clinical phenomena of organ specificity in metastasis (tumour preference for specific metastatic sites) and of tumour dormancy are reminders of the importance of the host response in metastatic malignancies. Only now are the tools adequate to explore these complex relationships at a cellular and molecular level.

Primary liver tumours provide an excellent model in which to explore tumour-host interactions. About half of them possess some degree of fibrous tumour encapsulation which has the appearance of limiting tumour invasion and patients with tumour encapsulation have a better prognosis than those without. We determined that the encapsulation response is due to hepatic myofibroblasts, the hepatic stellate cells (HSC) that become activated and are stimulated to proliferate at the tumour-liver interface by tumour secretion of platelet-derived growth factor. The curious paradox about this encapsulation is that whilst collagen is being laid down in abundance in the capsule, there is also active matrix metalloprotease activity at the same sites, which has the effect of degrading the collagen. We therefore proposed a hypothesis that in this tumour-host interaction, tumour-derived pro-fibrogenic factors (such as TGFβ) compete with collagen-degrading factors (such as MMPs) in a dynamic interaction, the ultimate balance of which determines whether encapsulation takes place. To test this hypothesis, we developed models of HCC in rodents and showed that if the balance was tipped towards decreased collagen degradation using systemically administered synthetic inhibitors of MMPs, the tumour capsule was thicker and tumour invasion less evident. This is an example of how the host response might be manipulated to produce a result that is favourable to the host.

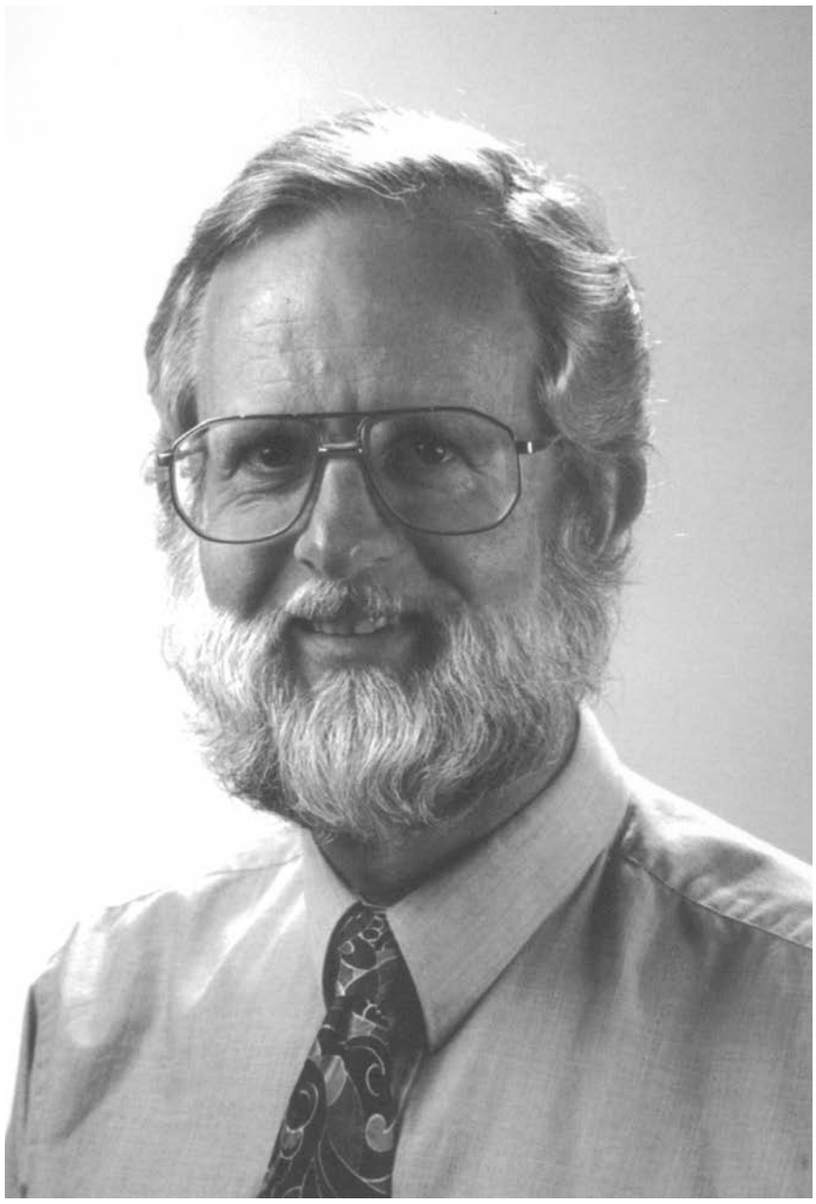
The HSC in the liver appear capable of elaborating a number of factors that are potentially capable influencing tumour behaviour, including potent angiogenesis stimulating factors (e.g. bFGF and VEGF) and tumour growth and motility factors (e.g. hepatocyte growth factor/scatter factor). Current research efforts are directed toward understanding aspects of the role HSC play in determining invasiveness of primary liver tumours, using HSC cells

freshly isolated from rat and human livers. Identification of host derived elements that are important for tumour invasion would enable much more effective targeting for therapy, since the host cells are a heterogeneous population that retain normal controls over cellular pathways.

Likewise, tumours metastatic to the liver must interact with normal host stroma in order to grow in "foreign soil". A classic example of this is angiogenesis, in which host endothelial cells are induced to form new blood vessels for the tumour to allow it to grow beyond 1-2mm. The most potent stimulator of this phenomenon is vascular endothelial growth factor (VEGF), expressed by both tumour cells and host stromal cells. We and others have shown clear evidence that the cell surface molecule CD44 has prometastatic capacity for many epithelial tumours, including colon cancer. Our studies have shown an abrogation of metastasis in a mouse colorectal tumour model when CD44 gene expression is suppressed in tumour cells. We have now adduced evidence of the mechanism for this: a discrete domain of the molecule that binds heparan sulphate has the capacity to bind heparin-binding growth factors such as HGF and VEGF and present them to definitive receptors on tumour cells and host stromal cells to provide a growth advantage. Mutation of this site in the gene that produces a change of a single amino acid is sufficient to abolish metastatic growth altogether.

This is an important finding since it is another potential pathway for therapeutic intervention in the treatment of occult or minimal residual disease in the liver and potentially at other sites. These and other such studies demonstrate the importance of the interrelation between tumour and host. The mechanisms are complex, but clearly provide fertile ground for the search for novel therapeutic modalities.

We are enormously grateful to the College for its support of this work through the John Mitchell Crouch Fellowship.



2000

Michael Valentine Agrez

Associate Professor, University of Newcastle

Colorectal cancer is the most common internal malignancy affecting our society; however, the molecular mechanisms responsible for progression of this disease remain largely unknown. Tumour progression reflects the ability of cancer cells to proliferate and degrade surrounding matrix barriers and these events are regulated, at least in part, by cell adhesion molecules and matrix-degrading enzymes such as matrix metalloproteinases. Amongst the many cell adhesion receptors, the family called integrins has been best characterised. Integrins are transmembrane receptors comprised of 2 subunit molecules (α and β) which together provide a structural and functional bridge between the external matrix environment and intracellular cytoskeletal and signalling molecules. For many years now, the major research focus in our laboratory has been the role of one particular integrin, called $\alpha v\beta 6$, in the growth of colon cancer.

More recently, we have made the discovery that expression of this growth-promoting integrin, $\alpha v\beta 6$, in colon cancer cells leads to increased secretion of the matrix-degrading enzyme, matrix metalloproteinase-9 (MMP-9) capable of digesting various collagens and other extracellular matrix molecules. More importantly, biochemical inhibition of MMP-9 activity abrogates $\alpha v\beta 6$-mediated colon cancer growth. Given that $\alpha v\beta 6$ is not expressed in normal epithelial cells but becomes highly expressed during tumourigenesis, we asked whether the $\alpha v\beta 6$-MMP-9 growth-promoting axis might help cancer cells escape the growth constraints imposed upon normal cells by cell crowding and dense pericellular matrices.

Support through the John Mitchell Crouch Fellowship has made it possible to address this fundamental biological question in cancer resulting in the discovery that at high cell density, when proliferation of tumour cells slows down, $\alpha v\beta 6$ expression increases. As a consequence, MMP-9 secretion increases with cell crowding - but only in $\alpha v\beta 6$-expressing cells. This has led us to postulate the existence of a self-perpetuating model of colon cancer progression mediated through up-regulation of the $\alpha v\beta 6$-MMP-9 axis at high cell density. In this model, $\alpha v\beta 6$-mediated-MMP-9 secretion at high cell density results in pericellular matrix degradation, which facilitates tumour cell migration and restores low density conditions allowing tumour cells to resume active proliferation.

These findings then raised another question, namely, which intracellular signalling pathway(s) is involved in this cell density-dependent upregulation of $\alpha v\beta 6$ and MMP-9?

Amongst the family of intracellular signalling molecules known to be involved in regulating cancer growth in general are kinases which phosphorylate and, thereby, activate other growth-promoting genes. One major family of kinases, known as protein kinase C isoforms (PKCs) is known to regulate diverse cellular processes such as cell proliferation, differentiation, migration and invasion. However, nothing is known of the effect of high cell density on PKC activity in any epithelial cells – be they normal or malignant.

Support from the John Mitchell Crouch Fellowship has enabled this question to be addressed. The preferential increase in cell surface expression of the growth-promoting $\alpha v\beta 6$ integrin at high cell density over other integrins occurs in a PKC-dependent manner. Importantly, although PKC activity in colon cancer cells increases slightly with cell crowding in the absence of $\alpha v\beta 6$, a dramatic increase in PKC activity occurs at high cell density when the $\alpha v\beta 6$ integrin is present. Moreover, it is the $\alpha v\beta 6$-mediated increase in PKC activity which is responsible for the enhanced MMP-9 secretion by cancer cells at high cell density. These findings have been accepted for publication in the International Journal of Cancer (2001). Our next goal is to identify the growth-signalling molecules within cancer cells which interact either directly or indirectly with the $\alpha v\beta 6$ integrin. Given the dismal prognosis for colon cancer, and the adverse side effects of adjuvant therapy for advanced disease, these future studies will have important consequences for the design of novel therapeutic strategies targeting specific colon cancer cell characteristics.

2001

HERBERT KERR GRAHAM

Professor of Orthopaedic Surgery, University of Melbourne
Director of Hugh Williamson Gait Analysis Laboratory,
Director of Orthopaedic Surgery, Royal Children's Hospital, Melbourne

Background

The Hugh Williamson Gait Analysis Laboratory at the Royal Children's Hospital in Melbourne was the first facility in Australia to offer a clinical gait analysis service in a large children's hospital. Since the laboratory opened in 1995, it has had a pivotal role in the introduction of motion analysis within Victoria, Australia and New Zealand. Instructional courses have been held with both local and international visiting faculties leading to a rapid increase in instrumented gait analysis throughout Australasia and the establishment of motion analysis laboratories in each state within Australia and in New Zealand. The Hugh Williamson Gait Laboratory has an active clinical service program as well as a basic and applied research program. When surgeons and physiotherapists are introduced to the technicalities of instrumented gait analysis for the first time, the complexity of the biomechanics and the volume of new material can be overwhelming. In addition, there is a need to communicate the relevance of gait patterns to day to day management of children with motor disorders, to the wider medical and allied health community. We have therefore embarked on a program of investigation to devise a new biomechanically orientated classification of gait patterns in spastic diplegia.

Spastic diplegia is the most common form of cerebral palsy, which in turn is the most common physical disability in children in Australia and in most developed countries. The incidence is increasing because of the survival of low birth weight and very premature infants. These children usually have normal intelligence, a normal life span but are greatly hampered by their physical disabilities. Many new and effective treatment modalities exist to help children with spastic diplegia including selective dorsal rhizotomy for spasticity and single event multilevel orthopaedic surgery for the management of contractures and bony torsional abnormalities. However we perceived a need to devise a classification of gait patterns which would be relevant to management and help in the education of the large number of physicians, surgeons and allied health personnel who are involved in the care of these children.

Gait Laboratory Investigations

We conducted a cross-sectional and longitudinal study of all children with a confirmed diagnosis of spastic diplegia who had had a full three dimensional gait analysis at the Hugh Williamson Gait Laboratory during the past five years. We excluded children with other movement disorders and other fixed deformities which might corrupt the data. In addition, we identified a subset of children who had had more than one gait analysis, at least 12 months apart, with no surgical intervention in the interim. We used the information from this cohort to study longitudinal changes in gait patterns.

One hundred and eighty-seven children fulfilled the inclusion criteria for the cross-sectional study. From the analysis of sagittal plane kinematics we have established a new biomechanically orientated description of gait by comparing the child's kinematic data with our laboratory normal range. The new classification includes the following patterns: mild, true equinus, jump gait, apparent equinus, crouch gait, and asymmetric gait. These terms have been used loosely in the past but we have now applied them with a strict kinematic criteria supported by quantitative data analysis.

The significance of the new classification is that it is based on sound biomechanical principles. In moving from mild through to crouch gait, we noted the following characteristics:

- A progressive decrease in distal contractures and a progressive increase in proximal contractures
- A progressive decrease in the activity of the plantarflexion-knee extension couple
- A progressive redirection of the ground reaction force from in front of the knee to behind the knee
- Increasing incidence of dynamic knee stiffness during gait.
- Decreasing walking velocity
- Increased energy cost of walking
- Decreased function.

The new classification has direct relevance to spasticity management, multilevel orthopaedic surgery and the use of orthotic devices.

Thirty-four children were eligible for a longitudinal study of gait patterns and this has added to our knowledge of the natural history of gait patterns in spastic diplegia. It has provided further information on which to base successful management strategies.

Conclusion

We have devised a new classification of gait patterns in spastic diplegia which is based on quantitative data but is intuitive and relevant to management. Additional studies addressing the validity and repeatability of the classification are showing promising results. The classification has been widely accepted as being a useful template for teaching, research and intervention studies. The classification will be presented at two major international meetings this year and will be submitted shortly for publication.

The award of the John Mitchell Crouch Fellowship in 2001 has provided the funding and support for the research personnel involved, which includes a Research Physiotherapist and an Orthopaedic Fellow from India. One of the goals of the classification was to provide a template for surgeons who have no access to motion analysis, to apply management principles devised from motion analysis laboratories to their population. The support of the overseas Fellow and his involvement in this work has been crucial to this process.

The successful outcome of this work has laid a platform for a further project grant application to NH&MRC in the 2002 grant round.

2002

Spencer Wynyard Beasley

Clinical Professor of Paediatric Surgery, Christchurch School of Medicine, University of Otago
Chief of the Child Health Service, Canterbury District Health Board
Clinical Director, Department of Paediatric Surgery, Christchurch Hospital and Christchurch Women's Hospital

Congenital malformations of the foregut are common in the human (occurring in about one in 3,000 live births). Until recently, the processes that cause these abnormalities have been obscure, but we now realise that there are several genes that encode signalling molecules during embryogenesis, and the normal function of these signalling pathways may be important to enable the correct development of organs in the embryo. It appears that the sonic hedgehog (Shh) signalling pathway may play a crucial role in foregut development, and the Glil and Gli2 and Gli3 transcription factors are responsible for the activation and repression of hedgehog-target genes.

We performed a study to determine whether sonic hedgehog protein is expressed throughout the rat foregut during embryogenesis, and whether its level of expression varies at different embryonal stages. We also performed a study to determine whether Adriamycin (which produces foregut abnormalities very similar to those seen in the human) may influence this sonic hedgehog pathway.

The background to this study was based on a suspicion that the sonic hedgehog gene had a role to play in the differentiation of the foregut into the trachea and oesophagus. It has already been demonstrated in a variety of animals that it is expressed in the notochord, floor plate and endodermal epithelial organs (trachea, lungs and digestive tract). It is also known to be involved in first phase signalling from endoderm to mesoderm. Sonic hedgehog Shh /-mutant mice have oesophageal atresia and/or tracheo-oesophageal fistula, providing indirect confirmation for a critical role for the sonic hedgehog gene in the development of these organs.

The sonic hedgehog protein is secreted as an inactive precursor, and undergoes auto-proteolytic cleavage into amino and carboxy-terminal peptides. The amino-terminal peptide component remains associated with the surface of the cell whereas carboxy-terminal peptide diffuses away from the cell surface.

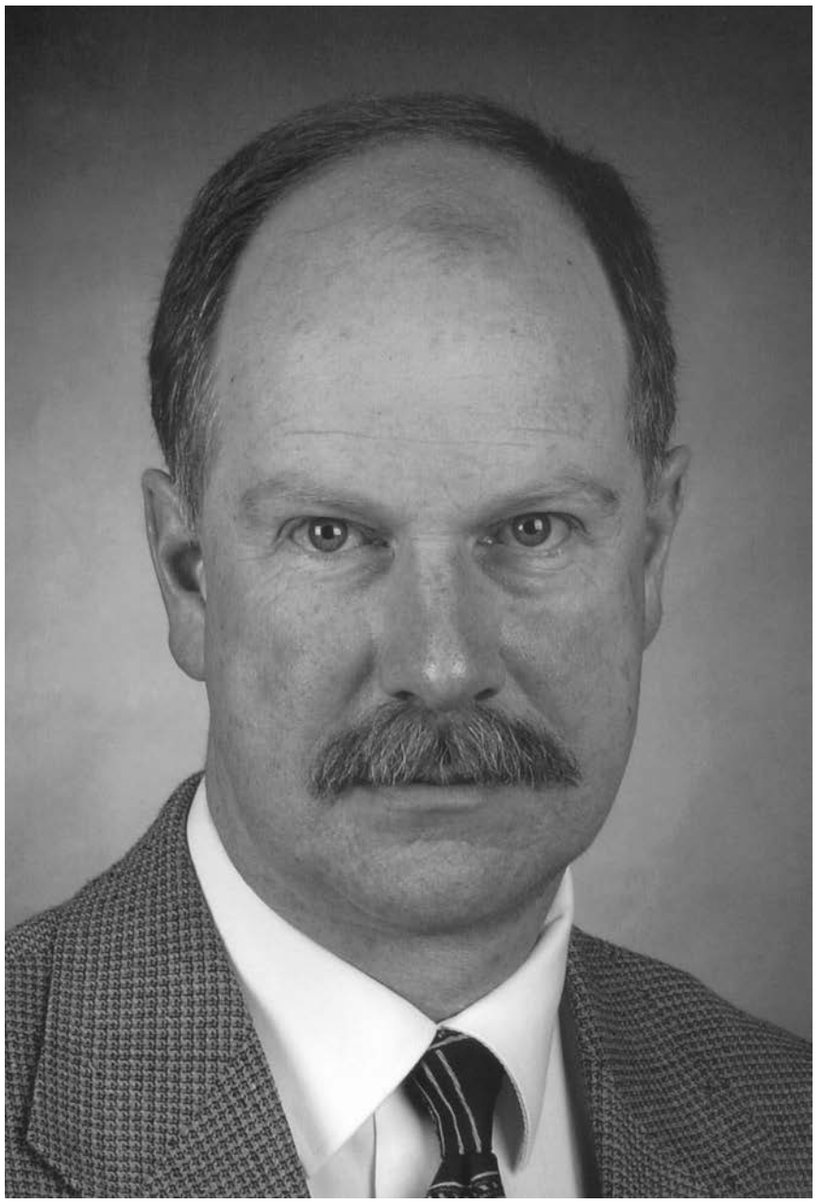
In our study, experimental rats received daily 1.75mg/kg Adriamycin by intra-peritoneal injection from gestational days six to nine. Control animals received saline only. The rat embryos were harvested by caesarean section between gestational days 10 and 15. Foreguts were dissected and total proteins extracted. The presence of sonic hedgehog protein was detected by immuno-blotting. The level of sonic hedgehog protein expression was determined by ELISA. Expression analysis of the sonic hedgehog gene was determined using PCR (polymerase chain reaction) at gestational days 12 and 13 in both the control and Adriamycin-treated embryos.

Analysis of our results confirmed that sonic hedgehog protein is present throughout foregut development. The level of Shh protein decreases once the foregut has differentiated into oesophagus, trachea and lungs. Levels of Shh protein in Adriamycin-treated animals are lower than that of control animals. The level of sonic hedgehog protein in Adriamycin-treated animals does not change during embryonal development.

From these studies it appears that lack of sonic hedgehog protein and its signalling components may be responsible for foregut defects in humans. Expression analysis of the sonic hedgehog gene implies that there is a significant change in the amount of sonic hedgehog amplified in the control and Adriamycin-treated embryos on days 12 and 13. Adriamycin might influence the sonic hedgehog pathway and disrupt normal development of the foregut, thus producing congenital abnormalities similar to those seen in the human.

It is our expectation that a similar sequence of events is responsible for anorectal and many vertebral anomalies. We are planning further studies to confirm this, as well as to better identify the downstream genes involved. Ultimately, identification of the factors that "turn off" the sonic hedgehog pathway may prove valuable in the treatment of cancers later in life (eg glioma, basal cell carcinoma, hepatoblastoma) where the sonic hedgehog pathway becomes inappropriately "turned on" again.

This work could not have been performed without the support of the John Mitchell Crouch Fellowship.



2003

David Ian Watson

Professor and Head, Department of Surgery, Flinders University of South Australia
Head of Gastrointestinal Services, Flinders Medical Centre

The John Mitchell Crouch Fellowship has provided support for ongoing research in my laboratory group within the broad areas of: 1) the development and prevention of oesophageal cancer, and 2) surgical treatment of gastro-oesophageal reflux disease. Common to these general areas is the condition Barrett's oesophagus, which entails metaplasia of the mucosa of the lower oesophagus. This results in the replacement of the normal squamous cell lining with an unstable columnar mucosa. This predisposes to the development of oesophageal adenocarcinoma in some individuals. Oesophageal adenocarcinoma is becoming increasing common in Western societies, including Australia and New Zealand. It is difficult to treat effectively, and it is associated with a low rate of cure. Furthermore surgical treatment is associated with a high rate of morbidity, and a significant mortality risk.

My department is conducting a program of randomised clinical trials which are evaluating various procedures for the treatment of reflux and Barrett's oesophagus. We have completed the recruitment phase for five randomised controlled trials which are investigating different laparoscopic techniques for surgery for gastro-oesophageal reflux. Four of the studies have involved patients undergoing surgery within Adelaide, and the fifth is a multi-centre randomised trial of total versus anterior 90° partial fundoplication, involving a collaboration of surgeons from all major cities within Australia, as well as Auckland, New Zealand. These trials have demonstrated that division of the short gastric blood vessels are unnecessary during total fundoplication, that an anterior 180° partial fundoplication outperforms a total fundoplication at 5 years follow-up, that the method of hiatal repair does not affect outcome following total fundoplication, and that an anterior 90° partial fundoplication is an effective surgical treatment for reflux which is associated with a low rate of side effects. We will continue to follow the patients in these trials long term to ensure that late outcomes are determined and reported.

Two further randomised clinical trials are evaluating the use of endoscopic argon beam plasma coagulation for ablation of Barrett's oesophagus, either in patients who are undergoing treatment of their gastro-oesophageal reflux with acid suppressing medications, or in patients who have undergone a successful surgical procedure for reflux. The early outcome of these trials has demonstrated that Barrett's oesophagus mucosa can be destroyed, and in the absence of ongoing reflux, the distal oesophageal mucosa will regenerate as a macroscopically normal appearing mucosa. However, this does not necessarily mean that the regenerated mucosa will be stable, and that the cancer risk associated with Barrett's oesophagus will be eliminated by this treatment. For this reason, these patients will be followed long term. In addition, we have added a molecular biology arm to these studies, and are now evaluating molecular markers and gene expression patterns to determine the source of cells which repopulate the mucosa following ablation, as well as the genetic stability of these cells. This work is in its early stages.

We are also collecting a large amount of fresh tissue biopsy material from the oesophageal mucosa during endoscopy procedures for various disease conditions. With this material we are now beginning to determine gene expression changes in cells lining the oesophagus which are associated with progression from normal oesophageal mucosa, to reflux oesophagitis, Barrett's oesophagus, dysplasia and eventually adenocarcinoma. This biopsy material is being analysed using DNA microarray analysis, other molecular biological techniques, and immunohistochemistry to identify and validate previously unidentified genetic changes in oesophageal mucosal cells which are associated with oesophageal cancer development. In addition, we are determining the effect of treatment of reflux, by both medical and surgical therapies, on the expression of genes in the oesophageal mucosa. Information about this will help to determine whether specific therapies for reflux are able to reverse precancerous gene expression changes, thereby guiding treatment decisions in individuals with gastro-oesophageal reflux. Ongoing work in this area aims to identify the sequence of events which are associated with oesophageal cancer development at the molecular level. When we have a better understanding of this process we expect that opportunities will arise to explore new treatment options for this disease.

The John Mitchell Crouch Fellowship has provided additional resources which have helped to fund new directions within this research program. It has provided funds for the initial studies which are needed to demonstrate the potential for success in new areas, and studies which should progress to new programs of research, supported by other funding bodies.

2004

Jeffrey Victor Rosenfeld

Professor and Head of Surgery, Central and Eastern Clinical School, Monash University.
Professor / Director Neurosurgery, The Alfred Hospital

The aim of my research is to improve the outcome of patients with traumatic brain injury and involves four projects:

1. The Intensive Monitoring of Patients with Traumatic Brain Injury (With Dr Alex Adamides and Prof DJ Cooper and Prof T Kossmann et al)

Individualised therapy for the patient with severe traumatic brain injury (TBI) has been developed in this study using multiple monitoring techniques. The aim is to reduce episodes of secondary brain injury and therefore improve outcome.

The monitoring techniques included intracranial pressure (ICP), brain oxygen ($PbrO_2$), jugular venous oxygen saturation (JvO_2). Cerebral blood flow (CBF) was assessed using trans-cranial Doppler (TCD) and computed tomographic (CT) perfusion scans. Cerebral autoregulation was continuously monitored using the Pressure Reactivity Index (PRX) which compares arterial pressure and intracranial pressure (ICP) waveforms. We have developed our own software for the PRX analysis which has enabled us to identify the limits of cerebral autoregulation in the individual patient and to target an 'ideal' cerebral perfusion pressure (CPP) for that individual, thus minimising the risk of further secondary brain injury.

Brain metabolite monitoring using microdialysis has been done for the first time in Australia in the clinical setting. A fine catheter is placed in the brain and minute samples of extracellular fluid from the severely injured brain are collected in small vials. Glucose, lactate, pyruvate, glycerol, and glutamate have been measured half-hourly. This data is being correlated with the other intensive monitoring data and is being correlated with the onset of ischaemia.

The results of the initial 'blinded' phase of the study which are based on approximately 1,000 hours of data from 10 severe TBI patients showed that secondary injury processes are common. Brain oxygen was below the ischaemic threshold (15 mm Hg) for over 17% of the time, and Cerebral Perfusion Pressure (CPP) was maintained below the accepted minimum (60 mm Hg) for over 15% of the time.

Treatment algorithms were subsequently developed which we are using to deliver targeted therapy for the individual patient. Targeted therapy is likely to have an increasing role in specialised intensive care units.

2. The Efficacy of Decompressive Craniectomy Following Severe Traumatic Brain Injury. (With Prof DJ Cooper, Prof T Kossmann et al)

Diffuse TBI often results in generalised brain swelling, increased ICP and poor outcome. Removing the front of the skull in an operation called decompressive craniectomy (DECRA) allows for brain expansion and a lowering of the ICP. The role and timing of this operation are controversial. We reported the first randomised controlled trial of DECRA for severe TBI in children. This is the first randomised controlled trial of early DECRA following severe TBI in adults and is a multi-centre study which is coordinated by the Alfred Hospital and now has 18 participating centres from Australia, New Zealand, Canada and Saudi Arabia. The aim of this study is to determine whether the outcome of patients with diffuse brain injury is improved by early DECRA. We are aiming for 200 patients to be entered by the end of 2007.

3. Neurogenesis in focal and diffuse animal models of traumatic brain injury. (With Dr X Han, Assoc Prof C. Morganti-Kossmann, N Bye et al.)

There are neural precursor cells in the brains of adult mammals which may differentiate into glial and neuronal cells. These cells reside in the sub-ventricular zone (SVZ), hippocampus and olfactory bulbs. In the first phase of the study, we identified the features of neurogenesis and glial cell proliferation in focal brain contusion and diffuse axonal injury (DAI) models of TBI in rodents at different time periods. We found that there is a significant increase in cell proliferation in the SVZ and hippocampus following focal injury, and in the SVZ following DAI. Only a small number of the proliferating cells were stained for neuronal markers. Most are identified as glial cells.

The second phase of this study aims to increase the number of neuronal precursors by using topical application of neurotrophic factors. We have succeeded in cannulating the lateral ventricle of rats with microcatheters placed using a stereotactic frame. We are now aiming to boost the number of neurons in the SVZ following TBI in the rat using infusions of Brain Derived Neurotrophic Factor (BDNF) or cytokines such as interleukin-6 (IL-6) into these microcatheters. These molecules have been shown previously to have neurogenic properties. Induction of the SVZ precursor cells to neuronal differentiation may improve brain repair following TBI and therefore have future application following TBI in humans.

4. The effect of severe traumatic brain injury in young children.

I have continued my collaboration with Professor Vicki Anderson and the Department of Psychology at the Royal Children's Hospital and the University of Melbourne to study the effects of TBI on the intellectual and psychosocial development of young children. We have found that the developmental milestones of the young child are profoundly disturbed by a severe TBI early in life. Attention and memory disorders are also common in this group of children.

2005

CHRISTOPHER CHRISTOPHI

Professor and Head, Department of Surgery, University of Melbourne, Austin Hospital

Targeting of the Tumor Vasculature

The focus of research in 2005 for the John Mitchell Crouch Scholarship was specific targeting of the tumor vasculature of colorectal liver metastases. This approach may be used as an alternative to or in conjunction with conventional chemotherapy. The research was laboratory based using a mouse model of colorectal liver metastases, previously characterized in our laboratory. Three strategies were utilized:

(a) Enhanced Permeability and Retention Effect (EPR)

Tumor vessels have increased permeability compared to normal vessels and exhibit the phenomena of "enhanced permeability and retention" to macromolecular chemotherapeutic agents. The EPR effect may be attributed to several factors. Apart from increased tumor vessel permeability, sluggish and variable tumor blood flow and increased local production of vascular permeability mediators contribute to this effect. In addition the absence of lymphatics leads to decreased clearance of agents thereby increasing their effect. The efficacy of drug delivery systems using macromolecular chemotherapy, synthesized by our collaborators (Prof. H. Maeda, Japan) was tested in a mouse model of colorectal liver metastases. The agent SMA Pirarubicin is a derivative of Doxorubicin and was shown to selective target tumor tissue in a ratio of 20:1 compared to normal tissue. Its efficacy and toxicity was significantly improved to free Pirarubicin. There was also a significant decrease in tumor numbers and tumor volume in the treated animals. The areas of tumor necrosis were also increased. There appeared a thin rim of viable tumor tissue at the periphery. A survival study indicated increased survival rates of treated animals as compared to controls.

One of the major mechanisms of action of the cytotoxic effect of Pirarubicin is the production of radical oxygen species (ROS) and also accounts for major systemic toxicity. Tumor specific targeting of SMA Pirarubicin allows the action of this drug to be locally increased by increasing the production of local ROS and also allow minimization of the systemic side effects. The local production of ROS may be increased by the use of hyperbaric oxygen therapy or by inhibiting a key enzyme Hemoxygenase I using an agent SMA ZnPP. Our initial studies have shown that the administration of hyperbaric oxygen therapy or ZnPP increases the area of tumor necrosis compared to SMA Pirarubicin alone. Toxicity was also reduced.

Further studies have focused on further effects of SMA Pirarubicin on the tumor microenvironment. Studies have included the patterns of tumour necrosis, microcirculatory changes, hypoxia, angiogenesis and endothelial apoptosis. There appears to be altered patterns of endothelial apoptosis. The increased levels of hypoxia appear to stimulate tumour angiogenesis (increased VEGF expression) which may potentially be a cause of tumour recurrence and treatment failure.

(b) Direct Targeting of Established Tumour Vasculature

A second therapeutic approach is utilizing unique characteristics of the established tumor vasculature to directly target the endothelial cells of tumor vessels by the use of vascular targeting agents (VTA). Small molecular VTA's exploit pathophysiological differences between normal and tumor endothelium to achieve selective occlusion of tumor vessels. The differences in tumor endothelium compared to normal tissue endothelium include increased proliferation, increased permeability and their reliance on a tubulin cytoskeleton to maintain cell shape.

Our work has concentrated on the Combrestatin family of drugs, including Combrestatin CA4P and a more potent agent Ox16C. These agents are potent inhibitors of tubulin polymerization leading to rearrangement of the cytoskeleton and endothelial cell shape. This causes vessel thrombosis leading to tumor hypoxia and necrosis.

These agents have been tested in a mouse model of colorectal liver metastases. The best tolerated dosing schedule on Day 14 and 18 post tumor induction was associated with a marked reduction in tumor volume compared to controls. A forty day survival study showed an increased survival compared to untreated animals. A single dose of these agents caused an acute dramatic reduction in blood flow within the first 24 hours following administration. Progressive vascular destruction was evident. Normal liver sinusoids, as well as renal, mesenteric and pulmonary blood flow were unaffected.

(c) Antiangiogenesis

A third therapeutic approach targeting the tumor vasculature is the prevention of formation of new tumor vessels or angiogenesis. We have focused on the role of the Renin Angiotensin System (RAS) and its effect on liver tumors. There is evidence that blockade of the RAS may have an effect on tumor growth possibly via anti angiogenic pathways. Possible pathways may include VEGF, ECM formation and MMP's.

Using the animal model of colorectal liver metastases, we have investigated the effect of ACE inhibition (Captopril) and blocking of the ATR1 receptor (Irbesartan) on tumor growth. Our initial results have shown a significant decrease in both the number of tumors and tumor volume of liver metastases using these agents. Further investigation regarding possible underlying mechanisms are been currently pursued.

In conclusion, targeting the tumor vasculature is an attractive alternative especially when used in conjunction with standard chemotherapy. This may be achieved by drug delivery systems using the EPR effect or agents directly targeting the mature tumor vessels (vascular targeting) or preventing the development of new tumor vessels (angiogenesis).

2006

Julian Anderson Smith

Professor of Surgery, Monash University
Head of Cardiothoracic Surgery Unit, Monash Medical Centre

Utilising funds made available in 2006 from the John Mitchell Crouch Fellowship, the following two projects were undertaken:

I. Determining Subtle Changes in Cognitive Function After Cardiac Surgery

Coronary artery bypass grafting (CABG) and valve repair/replacement surgery are known to be associated with subtle cognitive impairment post-operatively, but it is unclear whether these impairments exist prior to surgery or whether they occur as a transient complication of the surgical procedure. In addition, little is known about the cognitive affects of robotically-assisted valve surgery. This study examined the incidence of cognitive deficits in these patient groups using a novel computer based bedside test and a series of "gold standard" neuropsychological tests.

Four surgical groups were studied: (1) on pump CABG, (2) valve repair/replacement, (3) robotically-assisted mitral valve repair and (4) a non cardiac general thoracic surgical control group. Participants were assessed pre-operatively, 4-7 days post-operatively and 6 weeks post-operatively. Neuropsychological evaluation included measures assessed and information processing (computer-based task), verbal learning and memory (auditory verbal learning task), complex visuo-motor coordination (grooved PEG board), visuo-spatial ability and memory (complex figure task), and word fluency (controlled oral word association task).

The groups did not differ in age, education or pre-morbid IQ. The levels of depression, anxiety and stress at each of the testing sessions did not differ significantly between any of the surgical groups at any of the testing sessions. Data from our cognitive test battery revealed that compared to the non cardiac general thoracic control group CABG patients demonstrated impaired cognition before surgery, became significantly more impaired after the surgery and remained impaired six weeks post-operatively. In contrast, the valve repair/replacement and robotically-assisted valve surgery groups displayed better cognition prior to surgery, experienced some impairment one week after surgery, but had returned to the preoperative levels within six weeks.

These results showed that CABG patients have impaired cognition prior to surgery and that this impairment increases after surgery. It seems likely that coexistent cerebrovascular disease in the CABG group contributes to this impairment. Further studies are required to ascertain whether cognitive function is restored after longer recovery periods in these patients. The finding that both of the patient groups who received valve surgery demonstrated a similar transient impairment of cognitive function indicates that both surgical techniques provide an equally favourable cognitive outcome for the patient. However, it is unknown whether both forms of valve surgery are associated with equally good cognitive outcomes at longer recovery times.

2. Surgeons' Attitudes Toward and the Use of Evidence Based Medicine in Surgical Practice

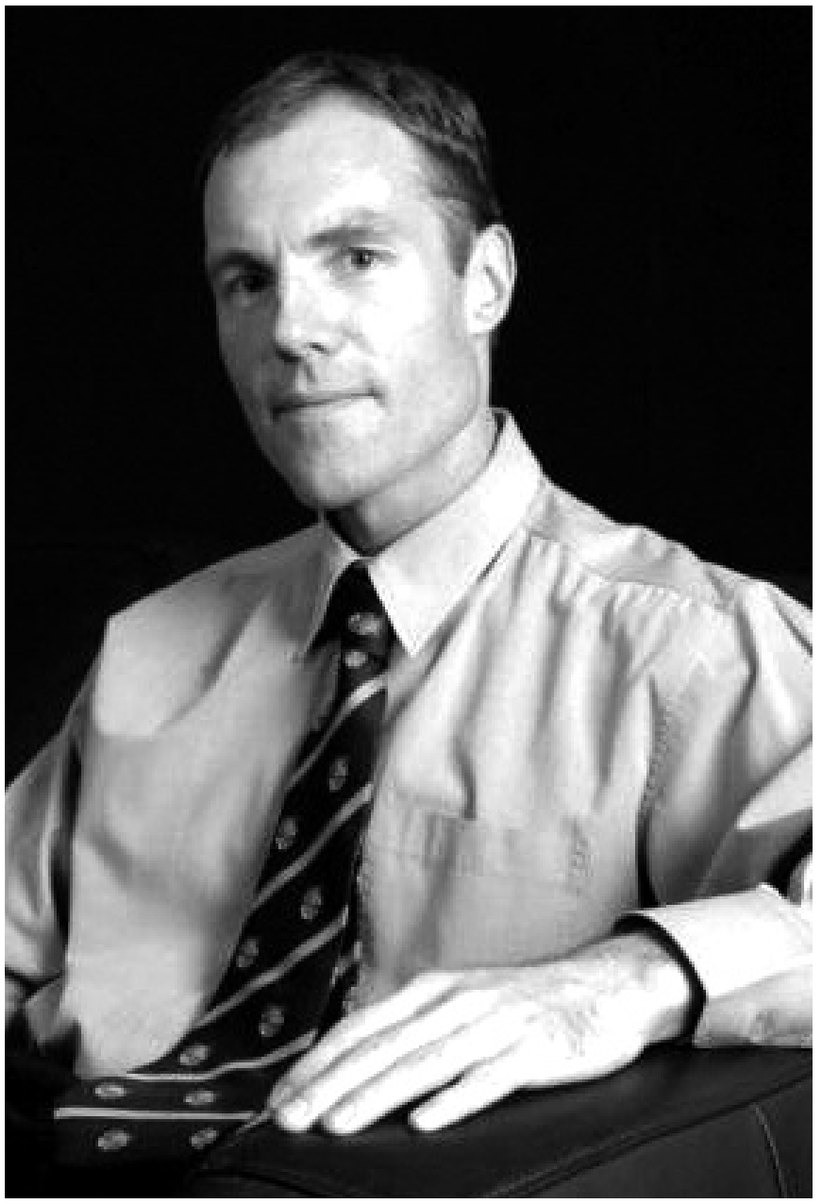
Evidence Based Medicine (EBM) refers to the utilisation of methods that have a strong scientific basis for clinical diagnosis and treatment. Within surgery, the debate about the place of EBM has focused on the nature and compatibility of EBM with various forms of surgical practice. Many surgical procedures actually lack a solid evidence base. In recent times EBM techniques have been imbedded into undergraduate medical curricula and surgical training programs across Australia and New Zealand.

The Monash University Department of Surgery at Monash Medical Centre recently implemented a pilot study to explore current knowledge, attitudes and behaviours of practicing surgeons towards EBM techniques. A detailed questionnaire was sent to 25 practicing surgeons across multiple surgical specialties at Southern Health. Following completion of the questionnaire, a more detailed one-on-one interview was conducted with each of the participating surgeons.

Our results revealed an ambivalent and contradictory attitude towards EBM in surgical practice. The results from the surgeons surveyed suggest they believe: (1) that EBM marginalises patient involvement in decision making, (2) that EBM generated knowledge is useful and is commonly used in daily clinical decision making – however not using EBM does not adversely affect a surgeons daily clinical decision making, (3) that surgeons have high confidence in their own clinical judgement compared with low confidence in clinical practice guidelines and other sources of evidence, and (4) that journal summaries of the latest research related to a subject are the most useful resources in clinical practice above clinical practice guidelines. It was also recognised that there is a definite "culture" of surgery which is important to consider when understanding and developing new ways to mobilise Australian surgeons to adopt EBM into their surgical practice.

Further studies are planned to ascertain whether these findings apply to all surgical specialties and also whether surgeons practicing in rural areas have similar attitudes. Findings from these studies will form the basis from which the development of future educational initiatives for surgical trainees and practicing may be launched.

Results of both the above projects have been presented at national meetings and manuscripts are in preparation for submission to refereed journals. Two students have been key participants in each project and PhD and MPhil theses are in preparation for submission to Monash University.



2007

Jonathan Golledge

Professor and Director of Vascular Surgery, The Townsville Hospital
Director of Queensland Research Centre for Peripheral Vascular Disease, James Cook University

Abdominal aortic aneurysm, pathogenesis, biomarkers and determinants of progression

The prevalence of abdominal aortic aneurysm (AAA) is 1-5% in men and 1% in women aged ≥65 years. Approximately 2000 patients undergo surgical repair of AAA annually in Australia. The widespread use of abdominal imaging and the increasing longevity are resulting in large numbers of asymptomatic individual being diagnosed with small AAAs (<50mm). Randomised trials indicate that surgical treatment of these small AAAs is not appropriate. Thus patients with aneurysms measuring 30-49 mm are presently monitored by yearly or six monthly ultrasound. The management of these patients with small aortic aneurysms is currently sub-optimal in a number of areas:

1. We have limited knowledge of the natural history of small aortic aneurysms. Based on four randomised trials we know that over a ten year follow-up approximately 70% of 40-49mm aortic aneurysms will expand to a size requiring surgical treatment. Our understanding of smaller aneurysms (<40mm) is extremely limited. In particular we do not currently understand clearly the role of co-morbidities, environmental and genetic factors in determining the progress of aortic weakening. Improved understanding of these areas would enhance our ability to better select appropriate candidates for surgical and conservative treatment and individualise follow-up protocols. This information would also aid in defining pathways likely to be of value in the development of drug-based medical treatments designed to slow progression of aortic weakening.

2. Currently there is no agreed medical therapy which has been shown convincingly to slow progression of aortic aneurysm in patients.

3. At present there are no recognised blood tests useful in defining the presence of AAA. Detection requires abdominal imaging which is not always practical.

Given these issues in the present management of abdominal aortic aneurysm we have developed a collaborative program in an attempt to generate progress in these areas. Specifically we have:

1. Commenced trials to assess the efficacy of medical therapies in limiting AAA progression.

2. Established a mice model of human aortic aneurysm in order to assess the role of different pathways and blocking these on aneurysm development.

3. Established a number of cohorts of patients with known aortic diameter to assess the serum biomarkers and genetic sites associated with the presence and growth of aortic aneurysm.

2008

Peter Fook Meng Choong

Professor, Department of Orthopaedic Surgery,
University Department of Surgery, St Vincent's Hospital, Melbourne

Our basic science programme focuses on the mechanisms of osteosarcoma growth and spread, and how these processes can be controlled by targeting specific genetic signals with small molecules. Our objectives are to improve current understanding of bone tumour biology and to translate this into new treatment strategies for reducing drug toxicities, improving survival and increasing the potential for limb sparing surgery.

Projects undertaken during 2008 with the aid of the John Mitchell Crouch Fellowship:

The role of RECK in the regulation of chondrosarcoma growth and metastasis.

Chondrosarcoma, like osteosarcoma, is a common primary malignant bone tumour arising from mesenchymal stem cells. It mainly affects the adult population in the 4th decade, and most commonly arises as a low to intermediate grade tumour. Nevertheless it carries significant mortality with an overall five year survival of between 64% and 77%. Multiple wide resections may be required in order to prevent local recurrence and metastasis, with major physiological, functional and psychological implications. Furthermore, chondrosarcoma often arises within complex anatomical sites like the skull base, spine, and pelvis, leaving the patient with either inoperable or incurable disease. Such dismal outcomes are compounded by a universal lack of response to chemotherapy or radiotherapy in chondrosarcoma. Molecular agents targeting specific sarcoma pathways hold promise for chondrosarcoma because such an approach is not dependent on the rapid turnover of cells seen in common cancers, and is based on reversing the exact mechanisms responsible for chondrosarcoma progression.

Reversion-inducing, cysteine-rich protein with Kazal motifs (RECK) is a newly discovered cell-membrane bound protein with anti-angiogenic, and anti-tumour invasion properties, and therefore may hold promise for the treatment of chondrosarcoma. It was initially discovered after screening a cDNA library for genes which caused reversion to a flat morphology in the human fibrosarcoma cell line NIH-3T3. Further research by Oh and colleagues, led to the discovery that RECK was critical for controlling the maturation of blood vessels. In the realm of oncology, this attribute is highly sought after to prevent leaky vessel networks developing within cancer and facilitating uncontrolled growth and metastasis via the bloodstream. Much of this anti-angiogenic action has been attributed to the inhibitory action of RECK on matrix metalloproteinases, MMP-2 and MMP-9, which break-down basement membranes by degrading type IV collagen.

In health, RECK is expressed by most cells in the body but notably, it is down-regulated in many common tumours including colorectal, breast, and prostate. It has also been shown that in the minority of tumours where RECK is not down-regulated, a more favourable prognosis is conferred. Our recent examination of RECK expression in human chondrosarcoma samples suggests that downregulation is the rule. As yet, there has been no evaluation of any therapeutic action of RECK in chondrosarcoma, and only limited in vitro data has been published for RECK in osteosarcoma.

Recently we have found that RECK transfection of osteosarcoma cells has a strong inhibitory effect on tumorigenesis, invasion of bone and lung metastasis within an orthotopic model developed within our department. In vitro work with RECK transfected chondrosarcoma cell lines suggests that similar in vivo chondrosarcoma results are likely. A promising therapeutic effect clinically is also predicted from the knowledge that RECK target proteins, MMP-2 and MMP-9, are found to be expressed in direct proportion to chondrosarcoma grade, and are likely to facilitate local invasion. Hence, there is a pressing need to evaluate the benefits of RECK over-expression in chondrosarcoma by quantifying its effect on local invasion, tumour angiogenesis and metastasis.

To analyse the molecular events that accompany chondrosarcoma formation, and therefore can be targeted for tumour manipulation, an appropriate in vivo platform was required. While there have been a number of animal-derived chondrosarcoma models published, comprising allograft tumour transplanted into the rat (Swarm rat chondrosarcoma) or the hamster, these models are less relevant to the human disease and have been more useful for evaluation of chondrosarcoma growth and histology than in developing novel therapeutic agents. The athymic nude mouse has enabled reliable human xenograft transplantation. A number of human chondrosarcoma cell lines have been successfully used to generate subcutaneous tumours in this species, including OUMS-27 and HCS-2/A. Although effective in demonstrating anti-tumour effects of a number of agents, the lack of a representative orthotopic model diminishes overall clinical relevance.

With funding through the John Mitchell Crouch Fellowship, my team has been successful in developing both periosteal and intratibial models of chondrosarcoma using the human cell line JJ012. To our knowledge, this is the most clinically relevant animal model of human chondrosarcoma available. In both periosteal and intratibial implantation sites, lung metastases occur, although more consistently in the periosteal model which grows more rapidly. While the intratibial site is the more clinically relevant, both implantation sites allow assessment of tumour-bone interactions, soft tissue invasion and angiogenesis. Radiographic features of the model also replicate the human disease. Our aim will be to evaluate the effects of RECK overexpression and other novel agents within this new chondrosarcoma model.

Development of DZ13 DNAzyme to inhibit the biology of osteosarcoma

DNAzymes are single-strand catalytic DNAs capable of target mRNA cleavage. Previously, Dz13 has been shown to reduce the growth of melanoma indirectly via anti-angiogenesis and squamous cell carcinomas directly. Dz13 downregulates c-jun (its specific target) levels in rapidly proliferating cells, for instance when cells are stimulated post-quiescence, when c-jun is elevated. More recently, my team showed that Dz13 inhibited the growth of both osteosarcoma and liposarcoma in orthotopic models in our lab. Our preliminary results show tumour growth inhibition for prostate, breast and OS in bone of mice by Dz13 when tumour cells were mixed with Dz13 pre-implantation.

With the support of the John Mitchell Crouch Fellowship, we were able to conduct studies that revealed that the c-jun DNAzyme, was capable of reducing growth of orthotopic bone and ectopic prostate cancer, breast cancer and osteosarcoma cell, induced apoptosis via activation of caspase-2 and its PIDDosomal counterparts - PIDD (p53-induced protein with a DD) and RAIDD (receptor-interacting protein (RIP)-associated ICH-1/CED-3 homologous protein with a death domain), and release of mitochondrial cytochrome C.

In vivo and in vitro, downregulation of c-jun was observed, though this was not directly the cause of the death in these cells as c-jun siRNA did not induce apoptosis in these cells. Intriguingly, RAIDD and PIDD silencing enhanced cytotoxicity of the DNAzyme to a panel of osteosarcoma cells. Our preliminary data shows that Dz13 is not toxic in vivo.

In addition to the above studies, the John Mitchell Crouch Fellowship allowed us to continue studies exploring the development of a drug delivery system (DDS) for administration of DNAzymes in vivo. A DDS for Dz13, incorporating a chitosan-based formulation of nanoparticles (NPs), was developed by our group. Chitosan is readily derived from chitin, which is abundant in nature in the exoskeleton of crustaceans and insects. Being a 'green' raw material, which is both biocompatible and biodegradable in vivo, as well as being relatively inexpensive, leads to its current attractiveness. We modified a formulation for plasmid DNA using the complex coercavation technique and have made a few changes recently to better characterise and optimise the platform technology. This includes increasing the pH of formulation from 5.7 to 6, after testing a variety of variables such as pH, chitosan concentration, and temperature. Dynamic light scattering (DLS) revealed that the NPs were approximately 350nm in hydrodynamic diameter close to that found using EM. Zeta-potential of the NPs was positive which would allow it to better approach the slightly anionic plasma membrane of cells (dns). The Dz13-NPs were stable for a month at room temperature, and even gained activity when stored at 4oC for that time but lost activity when stored in human or mouse sera. This indicated that these particles would be most suitable for locoregional administration, one that avoids unnecessary exposure to serum and is injected in proximity to the lesion site. These NPs do not induce adverse effects at either the bone or intramuscular sites, two potential areas where administration of Dz13 for bone tumour therapy may be attempted in human patients in future.

2009

Stephen John O'Leary

Chair of Academic Otolaryngology (William Gibson Professor), University of Melbourne
Senior Otolaryngologist, Royal Victorian Eye and Ear Hospital

Simulation as a tool has been used by the aviation industry for many years and is a pre-requisite to pilot certification. In surgery however, the uptake has been much slower, largely due to success of the apprenticeship model of surgical training. It has become increasingly apparent that the curtailing of working hours and the increasing number of surgical trainees, young surgeons have less clinical exposure. Over the last year we have conducted experiments with young surgical trainees to determine the efficacy of 3D and virtual reality surgical environments as a training tool.

It has been demonstrated that simulators can differentiate between surgeons of differing levels of experience performing a temporal bond dissection. A further development has been the recognition that simulators can differentiate between novices and surgical registrars, demonstrating it is possible in the future to provide both feedback to surgeons during their training and also summative assessment of surgical skill. We have also demonstrated that training on a simulator leads to a better, real work cadaver dissection than conventional education.

The second achievement of the John Mitchell Crouch Fellowship was to bring to clinical translation the preservation of inner ear function in cochlear implantation. Even with the best electrode designs and the best surgical technique there are still significant numbers of patients who lose their residual hearing during implantation. If this natural hearing can be preserved it will successfully combine with the implant, to provide a better understanding of speech in the presence of background noise and a better appreciation of music.

We have investigated the possibility of preventing this loss through the application of protective drugs to the ear at the time of surgery. Over the last year we have demonstrated that an intravenous injection of a glucocorticosteroid prior to implantation protects hearing during experimental cochlear implantation. The John Mitchell Crouch Fellowship has also helped immensely in nearing the completion of our first clinical trial in inner ear protection. It is anticipated that protection of the inner ear with medication will become a standard part of cochlear implant surgery in the future.

2010

Damien Michael Bolton

Urologist

In 2010 I was fortunate to be awarded the John Mitchell Crouch Fellowship to assist my ongoing research in urologic oncology. The provision of this award has assisted this work in both objective and subjective ways, which I am pleased to be able to detail as follows.

One of the key projects in which I have a particular interest is the impact of BRCA2 gene positivity on clinical outcomes in prostate cancer. Previous work undertaken and published by our group on this topic has demonstrated a significantly greater risk of disease specific mortality for those patients with this genetic mutation. To further evaluate this issue a research fellowship was provided to an intending surgical trainee using the funds made available through the John Mitchell Crouch Fellowship. In 2011 Dr Liam Kavanagh joined our team to work on this topic. In his role as a full time research student in this area supervised by myself he undertook an evaluation of the role of prostatic intraepithelial neoplasia as a mediator of a cancer phenotype in BRCA2 mutation positive patients with prostate cancer.

As part of this project laser microdissection was undertaken of areas of prostatic intraepithelial neoplasia in samples of prostate cancer from patients with known BRCA2 mutation. Dr Kavanagh was taught this valuable research technique and extracted samples of the tissue were sent for genetic microarray analysis. Contrary to what we had presumed this work has suggested a less significant role for prostatic intraepithelial neoplasia as a precursor of prostate cancer in patients with known BRCA2 mutation. Some subtleties of prostatic intraepithelial neoplasia demonstration will be evaluated further as a direct consequence of this work, but in particular we have strong evidence that we should be focusing our research on alternate pathways of tumour development.

Equally importantly as a result of this work has been the experience obtained by our research fellow who will one day also be able to confidently undertake similar laboratory based genetic studies with the credibility and capability required to achieve a successful career in academic surgery.

In addition a further aspect of our research in urologic oncology has been the evaluation of the importance of tumour ischaemia and hypoxia in up-regulation of angiogenesis in renal carcinoma. As a result of the support obtained through the John Mitchell Crouch Fellowship I was able to support the ongoing study towards the degree of Doctor of Medical Science through the University of Melbourne of an accredited surgical trainee, Dr Kapil Sethi, who took time out from his clinical studies to undertake full time research on this topic. Specific evaluation has been undertaken of the role of cobalt preconditioning in prevention of progression through angiogenesis pathways, suggesting that this treatment which is paralleled in other aspects of surgical oncology may have relevance in respect of renal cancer also. This work has been subsequently accepted for presentation at multiple international urologic and basic scientific meetings, and will form the basis of an application for ongoing funding via the National Health and Medical Research Council (NHMRC).

Similarly as a consequence of this work I have noted the progression of Dr Sethi from an inexperienced researcher to a capable and highly respected author of valuable manuscripts that contribute significantly to the body of knowledge in this field. I am confident that an additional potential surgical researcher of repute in Dr Sethi has been uncovered and encouraged in this manner as a consequence of the support of this grant.

It has been a privilege to be the recipient of the John Mitchell Crouch Fellowship. This grant has greatly enhanced my research work both in the ways outlined above, and also by means of the additional attention that has been placed on my study as a consequence of being the first urologist to receive this award. I am greatly indebted to the Royal Australasian College of Surgeons for this opportunity, and hope that my ongoing work progressing from these recent areas of investigation will be successful enough to further justify the provision of this award.

2011

David Graham Little

Professor, Senior Staff Specialist, The Children's Hospital at Westmead

Utilising funds from the John Mitchell Crouch Fellowship, we expanded our research in two key areas.

1. Cellular contributions to bone repair.

Open fractures and high energy injuries have a high risk delayed union and non-union, which can affect up to 10% of cases. Even with agents such as bone morphogenetic proteins (BMPs) that can generate significant amounts of new bone, the treatment of serious fractures remains challenging. Direct hospital costs are A$12,000 per non-union, with a far greater socioeconomic cost. Critically, the exact cellular origin of the tissues that make up fracture callus remains unknown. Most accept that in uncomplicated closed fractures, the periosteum provides all the requisite cellular and vascular contributions required. There is currently no specific way to track the cells from the periosteum, which display several common mesenchymal markers.

In open fractures the periosteum is destroyed. However, some of these fractures heal, and others attempt to, pointing to other secondary sources of bone forming cells.

We have focussed thus far on muscle contribution to open fracture repair. We have utilised a MyoD-cre/Z/AP reporter mouse. In this double transgenic mouse strain, cells that have at any time expressed the master muscle commitment transcription factor MyoD can be tracked, even after trans-differentiation into another cell type. We have shown and published that myogenic cells do not directly contribute to the repair of closed fractures, but appear involved in open fractures healing where the periosteum is absent (Liu R, Birke O, Morse A, Peacock L, Mikulec K, Little DG, Schindeler A. Myogenic progenitors contribute to open but not closed fracture repair. BMC Musculoskelet Disord. 2011; 12:288).

With this funding we have further advanced our model systems. We have sourced, bred and optimised mouse strains where MyoD-cre is again used to label cells, now with an enhanced green fluorescent protein (eGFP) reporter via the Z/EG reporter strain. Using eGFP provides a number of advantages such as removing the requirement for staining (cells can be visualised immediately under fluorescence microscopy) and an ability to co-immunostain for other lineage markers. In this way, cells that label for bone and cartilage markers and eGFP represent cells that have undergone a bona-fide trans-differentiation event form a muscle cell into a osteoblast or chondrocyte.

In addition, we have sourced and bred Tie2-cre Z/EG reporter mice that enable us to track the contribution of vascular endothelial cells to fracture healing in the same system. Preliminary results using this system show abundant eGFP cells within the fracture callus and we are currently carrying out co-labelling experiments to determine whether these cells have remained vascular or have assumed an alternative lineage.

Lastly, the funds have enabled us to breed mice with which we can perform more functional experiments. We now have mice where we can abrogate the ability of the cells to transdifferentiate. Thus, in say a Tie2-cre mouse, we can (i) track vascular endothelial cells (ii) retain their ability to form blood vessels, their primary function and (iii) abrogate their ability to transdifferentiate into cartilage and/or bone. Thus, while we know these progenitors are present in fracture callus, this system allows us to know if their participation was functionally critical.

As further tools become available we will be able to identify the cell population most critical to successful repair, and look at therapeutic interventions specifically designed to advance this process and thus improve outcomes in open and high energy fractures.

2. Bone Tissue Engineering

Our laboratory has focussed for some time on the modulation of anabolic (bone forming) and catabolic (bone resorbing) processes in bone repair. It is logical that all bone formation is the sum of these two basic biological activities (Little DG, Ramachandran M, Schindeler A. The anabolic and catabolic responses in bone repair. J Bone Joint Surg Br. 2007; 89:425-33). We have previously proven, especially in stress-shielded environments, such as present with fixation of fractures, that bone resorption can predominate over formation, resulting in osteopenia.

We have begun translating these concepts to the field of bone tissue engineering. Here, scaffolds or even injectable systems are used to create bone either in its native site or even in an ectopic site for later transfer (say from an unhealthy to healthy tissue area). We have been utilising a resorbable scaffold made of poly lactic acid-co-glycolic acid (PLGA) which can be fabricated into a porous structure. This fabrication has been carried out in collaboration with Australian Institute for Bioengineering and Nanotechnology (AIBN) at the University of Queensland. This technology allows for a highly porous, resorbable substrate but with no native osteogenic potential. Recombinant human bone morphogenetic proteins (rhBMPs) are agents already approved for therapeutic use in humans, but current delivery systems are suboptimal. By incorporating rhBMPs scaffolds including our porous PLGA scaffold can be made osteogenic. Surgical studies in rodents have shown that, with rhBMP-2 addition, bone can be made in muscle de novo and the porous scaffolds were significantly more osteogenic than non-porous scaffolds.

However, the problem of stress shielding was still evident. We then went on to co-deliver rhBMP-2 with anti-catabolic drugs, both Zoledronic acid, a bisphosphonate, and a member of a drug class called IKK inhibitors, which inhibit osteoclast production. Both of these approaches yielded significant increases of bone formed. Bisphosphonate delivery was further refined by adding hydroxyapatite nano-particles to the polymer. As bisphosphonates bind to hydroxyapatite (HA), this ensures local retention.

These approaches were finally tested in a critical defect model. In this model, 5mm of bone is removed from a rat femur, and the gap held with a plate. Controls do not heal this defect. Adding Bone Morphogenetic Protein (BMP) in the standard collagen sponge used clinically resulted in healing, but the use of our polymer approach combined with anti-catabolic drugs led to a further increase in net bone formation and better healing of the defects. These studies confirm that controlling both bone formation and resorption is feasible in tissue engineering implants, and is likely to be superior to current approaches.

Commencing in 2012 we have gained National Health and Medical Research Council (NHMRC) research funding to carry on with this work, largely based on pilot data co-funded by the John Mitchell Crouch Fellowship.

2012

Marcus Andrew Stoodley

Professor of Neurosurgery, Australian School of Advanced Medicine, Macquarie University

Research in the neurosurgery laboratory at the Australian School of Advanced Medicine at Macquarie University during 2012 encompassed two main projects. In each of these projects, the focus was on developing new in vivo optical molecular imaging techniques that are crucial in advancing the field in each of these areas.

1. Developing new treatments for brain arteriovenous malformations (AVMs)

Our overall goal in this project is to develop a new treatment for high grade brain AVMs that are untreatable using current methods. Our proposal is to use a two-step process. In the first step, stereotactic radiosurgery is used to stimulate molecular changes on the surface of endothelial cells in the AVM vessels. The second step is to target those molecules with antibodies attached to molecules that stimulate intravascular thrombosis (such as tissue factor). We have previously demonstrated that this approach is feasible and our current work is aimed at identifying the best endothelial surface molecules to target with this therapy. An animal model of AVM treated with radiosurgery has been developed to study the early endothelial molecular changes that occur after radiation. Identifying the external membrane surface proteins is difficult: membrane proteins account for only 1% of the cell protein content. We have previously studied tissue removed at various stages after radiosurgery to assess membrane changes using immunohistochemistry and proteomic techniques and have identified several prospective target molecules. However, before developing pro-thrombotic treatments targeting these molecules, two aspects of the radiation response need to be determined. First, the quantity and time course of expression on the endothelial surface must be such that the targeted endothelium is highly differentiated from normal endothelium and the duration of increased expression is known. Second, for a molecule to be targeted safely, it must be expressed only in the radiosurgery-treated tissue and not in surrounding normal tissue. Assessing each of these aspects using molecular techniques on removed tissue is extremely difficult, if not impossible.

During 2012 we worked to develop in vivo molecular imaging techniques to study each of these aspects of radiation-induced endothelial molecular changes. First, we used endothelial tissue cultures treated with radiation to show that we could image live cells with fluorescent-labelled antibodies to molecules such as phosphatidylserine (PS) and E-selectin. We then applied these techniques to the rodent model of AVM. After delivering radiosurgery to the AVM, we used fluorescent-labelled antibodies administered systemically to image changes in PS and Intercellular Adhesion Molecule (ICAM) using a Multispectral In Vivo Imaging System. This technology had not previously been applied to study endothelial molecular changes after radiation. We were able to demonstrate that this technique provides quantitative information about molecular changes. Each animal can be imaged multiple times after radiation, which facilitates study of the time course of expression changes. We also showed that the changes in each of these molecules were restricted to the volume of tissue treated with radiosurgery and that the magnitude of change closely mirrored the radiation dose.

Our success in developing this technique enabled us to obtain National Health and Medical Research Council (NHMRC) funding for a comprehensive study of the quantitative changes and the anatomical location of expression of specific endothelial molecules in the animal model. At the completion of this phase of the project we will have identified highly prospective molecules for pro-thrombotic therapy. The next step will be to develop the thrombotic treatment agents and trial these in the animal model before progressing to human trials.

2. Understanding the pathophysiology of syringomyelia

One of the most enigmatic neurological conditions is syringomyelia, where fluid cysts form within the spinal cord. The origin of this fluid and the mechanism of cyst formation have remained obscure. It is assumed that the fluid is cerebrospinal fluid (CSF), but this has not been proven. We have been using animal models of syringomyelia and spinal cord injury to study the flow of CSF in the spinal subarachnoid space and in the spinal cord. Study using traditional fluid tracers requires rapid fixation of the animal and removal of tissue for histological study. It has not been possible to study CSF flow in live animals, and it has not been possible to quantify fluid flow in the subarachnoid space and spinal cord using these techniques. This has made it difficult to study the effects of various pathologies such as spinal cord compression and injury.

Building on the techniques developed in the AVM project, we developed techniques for studying CSF movement using the in vivo imaging system. The techniques developed allow quantitative assessment of fluid flow in the subarachnoid space and the spinal cord in the same animal. This is facilitating study of the effects of obstructions of the subarachnoid space such as external compression and arachnoiditis, which are potent causes of syringomyelia. The technique will also enable quantification of fluid flow out of the spinal cord, allowing us for the first time to study the balance between CSF flow into and out of the cord.

2013

Russell Lindsay Gruen

Professor of Surgery & Public Health, Monash University
Director of the National Trauma Research Institute, The Alfred.

The John Mitchell Crouch Fellowship has enabled some important research on the relationship between surgery and 'haemostasis,' or blood clotting. The ability of blood to clot is fundamental to surgery, and the physiology underlying it is very complex. In the normal state, there is a natural balance between the formation of blood clots, and their breakdown. Without these active processes constantly at work, we would bleed to death from relatively minor injury and surgery would be impossible, or we would develop harmful clots leading to strokes, myocardial infarction and pulmonary emboli.

The balance between clot formation and dissolution can be affected in a variety of ways. Increasingly surgeons treat patients who take long-term anti-thrombotic medications to 'thin the blood' by interfering with clotting – an 'exogenous' cause of predisposition to bleeding. It is now also realised that surgery and major trauma can, in themselves, alter the mechanisms of clot formation and clot dissolution and are 'endogenous' causes of coagulopathy. The mechanisms and the occurrence of these states are poorly understood. Better understanding of these mechanisms is likely to improve the safety of surgery, by reducing the risks of both unwanted intraoperative and postoperative bleeding, and postoperative arteriovenous thromboembolism.

As Director of the National Trauma Research Institute at The Alfred in Melbourne, and Professor of Surgery and Public Health at Monash University, where I work closely with the Australian Centre for Blood Diseases, I am ideally situated, along with my colleagues, to study these problems. We have a large patient base, connections to a network of like-minded clinicians across the country, access to broad multidisciplinary expertise in relevant areas, and excellent laboratory resources. We utilised this position to explore two main areas: in emergency surgery we are studying the tendency for severely injured patients to bleed because they have diminished clotting ability (exactly what you don't want if you're injured and bleeding); and in elective surgery we are studying the risks of bleeding and thrombosis associated with long-term antithrombotic medication.

The John Mitchell Crouch Fellowship has enabled us to successfully obtain National Health and Medical Research Council (NHMRC) funding for the PATCH-Trauma Study, a major international trial examining the effects of tranexamic acid (TxA) on fibrinolysis, inflammation and immune function following trauma. TxA was found fifty years ago to competitively inhibit conversion of plasminogen to the active protease, plasmin, thereby inhibiting fibrinolysis and clot breakdown but was little used in trauma care until the publication of the landmark 2010 CRASH-2 study, which found an almost ten percent reduction in trauma deaths in patients who received the drug on arrival at hospital, mostly in developing countries. While this was an important study with an important result, we were concerned that this study may not be as relevant as initially thought to severely injured patients in Australia, who are treated in advanced trauma systems. We were worried that we mightn't see the mortality benefits, and might see increased rates of thrombosis in patients treated with TxA.

There is a clear and widely acknowledged need for a robust clinical trial of TxA in advanced trauma systems, with both laboratory and clinical measures, to see whether or not we should be using this drug in trauma care and how it is changing the response to injury. Understanding all of this could change the management of almost 10,000 severely injured patients in Australia and New Zealand every year. The PATCH-Trauma Study is enrolling 1200 patients in Australian and New Zealand over four years. It engages ambulance and helicopter services and the trauma centres.

On the elective surgery front, we are studying the best way to manage antithrombotic medications around the time of surgery – whether they should be stopped and, if so, when they should be restarted. A variety of perioperative approaches are being used for the different anticoagulant and antiplatelet drugs, but a significant and unacceptably high number of patients still suffer post-operative bleeding, despite these protocols. Some of these patients needed readmission to hospital or repeat surgery. If we can understand this process and the best way to manage or counteract anti-coagulation agents, surgeons across all specialties will be better placed to prepare patients for both elective and emergency surgery and reduce the risk of post-operative bleeding.

This is a field where new drugs are emerging, many of which don't have a simple reversing 'antidote', and where the risks of stopping the medication to minimise bleeding during surgery need to be balanced against the increased risks of stroke or myocardial infarction. We simply don't yet know what is currently happening – how patients are currently being managed, and what the actual rates of bleeding and thrombosis are. Our research aims to establish some baseline data across a range of specialties in both public and private hospitals to see in preparation for a future trial of optimal strategies.

I believe we should be doing our best to conduct game-changing research. A great deal of preparation is required, before major national grants will even be considered. This work includes conducting background research, designing trials and forming synergistic partnerships and much of that would be impossible without such funding as that provided by the John Mitchell Crouch Fellowship. Furthermore it has supported the vision of academic surgery to which I subscribe, that is to combine surgical skills with an enquiring mind to improve the outcomes for surgical patients - in this case both trauma and elective patients across all surgical specialties.

2014

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Abdominal Surgery-Two wounds, not One

The experience of major abdominal surgery for the patient is dominated by pain, fatigue, loss of control, inability to eat, disturbance of circadian rhythms, lack of sleep and mixed emotions including anxiety and fear. Even following successful discharge from hospital and successful healing of all external wounds, the patient continues to feel tired, despondent and lacking energy to carry out usual daily tasks for up to three months.

In abdominal surgery two wounds are created. Firstly, a wound (somatic wound) is made in the abdominal wall in order to access the abdominal viscera. It is proposed that understanding the other wounds created: the peritoneal and visceral wounds, collectively making up the autonomic wound, are of vital importance where the disruption to these is great, such as after colectomy.

The abdominal wall is innervated by the thoracolumbar nerves from the anterior rami of various roots, projecting from the posterior column of the spinal cord. The effect of the somatic wound, whatever the size, is able to be "clinically controlled" by neural-axial blockade such as epidural anaesthesia. This provides excellent pain relief and decreases catabolism after colectomy. As a result the somatic wound has historically been uppermost in the minds of surgeons and anaesthetists. This focus on the somatic wound has found expression in the ever-developing field of minimal access surgery that has led to the possibility of virtually incisionless abdominal surgery.

When one considers procedures where the incision is the cause of the predominant metabolic insult to the patient, for example cholecystectomy, the benefits of a minimal access laparoscopic approach are obvious compared to classical open cholecystectomy. However, the advantages of a small somatic wound do not seem to be as obvious where concomitant large visceral disruption is required to achieve surgical outcomes. Laparoscopic colonic surgery, where the somatic wound is minimised, has only marginal clinical benefits over open colonic surgery. In non-optimised and non-blinded settings this benefit may be detected with a modest reduction in hospital stay. However, in optimised double-blinded peri-operative care settings (where evidence based clinical pathways are utilised to provide standard perioperative care), recovery after colectomy is not detectably different when laparoscopy is compared to open surgery. It is therefore postulated that the somatic wound impact may not be as important, in the greater scheme, on the post colectomy clinical state as previously thought. Thus, other factors may be at play, in order to explain the prolonged convalescence after major trans-peritoneal surgery.

The peritoneum is a high metabolically active sheet of tissue that envelops the majority of the abdominal viscera. This living sheet conveys sensory fibres via the vagus, which bypasses spinal cord blockade utilised by anaesthetists and surgeons to block afferent signals from the somatic wound.

The vagus nerve is the largest visceral sensory nerve in the body with approximately 50,000 afferent fibres, most of which innervate the peritoneum. Ninety percent of the subdiaphragmatic vagus is afferent in nature, indicating an important role in direct peritoneal to CNS signal transmission. Thus, vagal inputs originating from the peritoneum have great potential to modulate and regulate behavior in humans.

The systemic pro-inflammatory marker concentrations traditionally utilised to assess the inflammatory effect of major abdominal surgery represent only a small fraction of that generated from the peritoneum. The peritoneal cytokine levels are similar in laparoscopic and open colonic surgery. This suggests that in humans the two approaches are equally traumatic in their effect on the peritoneum and viscera and that the somatic wound is relatively minor compared to the autonomic wound in this context.

What seems to be important in abdominal surgery, is the extent to which the peritoneum is itself entered, dissected and manipulated. This is demonstrated by trans-peritoneal aneurysmal repair resulting in a significantly higher inflammatory response and slower clinical recovery compared to the extra-peritoneal approach. Therefore it is probable that the autonomic wound is the greater contributor to the overall metabolic response and clinical picture after major trans-peritoneal abdominal surgery.

A thoracic epidural may block some of the peritoneal and visceral nociception through splanchnic nerves that traverse the dorsal column of the spinal cord. However gastrointestinal afferent pathways constitute only 7-10% of all inflow to the cord, with the vagus nerve carrying by far the majority of the peritoneal and visceral nociceptor message to the CNS. This is supported by animal studies that have demonstrated that vagal afferents respond to mechanical and chemical stimulation and that these signals lead to brain stem activation. Vagotomy blunts this response but spinal cord transection does not.

The challenge that the autonomic wound presents to the surgeon and anaesthetist is substantial. Vagotomy in humans in this context is unethical but we have demonstrated that it is possible to perform a transient chemical afferentectomy with intraperitoneal local anaesthetic with short-term benefits in postoperative recovery. We have also shown that it is possible to partially dampen the local abdominal inflammation with glucocorticoids and that this is associated with measurable clinical benefits.

Putting the hypothesis into clinical practice

The surgical insult to the peritoneal cavity and viscera has not been emphasised as an important entity and a target for interventions. This autonomic wound has not been addressed as successfully as the peripheral somatic wound. It may be, in the foreseeable future, that the somatic wound can be almost be completely be dispensed with. Therefore, the autonomic wound created by the surgeon, and its downstream effects, will require much more attention.

The John Mitchell Crouch Fellowship has been of critical importance in developing a mechanism to provide prolonged autonomic blockade following major abdominal surgery. We have made significant progress in developing a mechanism to block vagal afferents over the last twelve months and hope to be able to run clinical trials in late 2015 or early 2016.