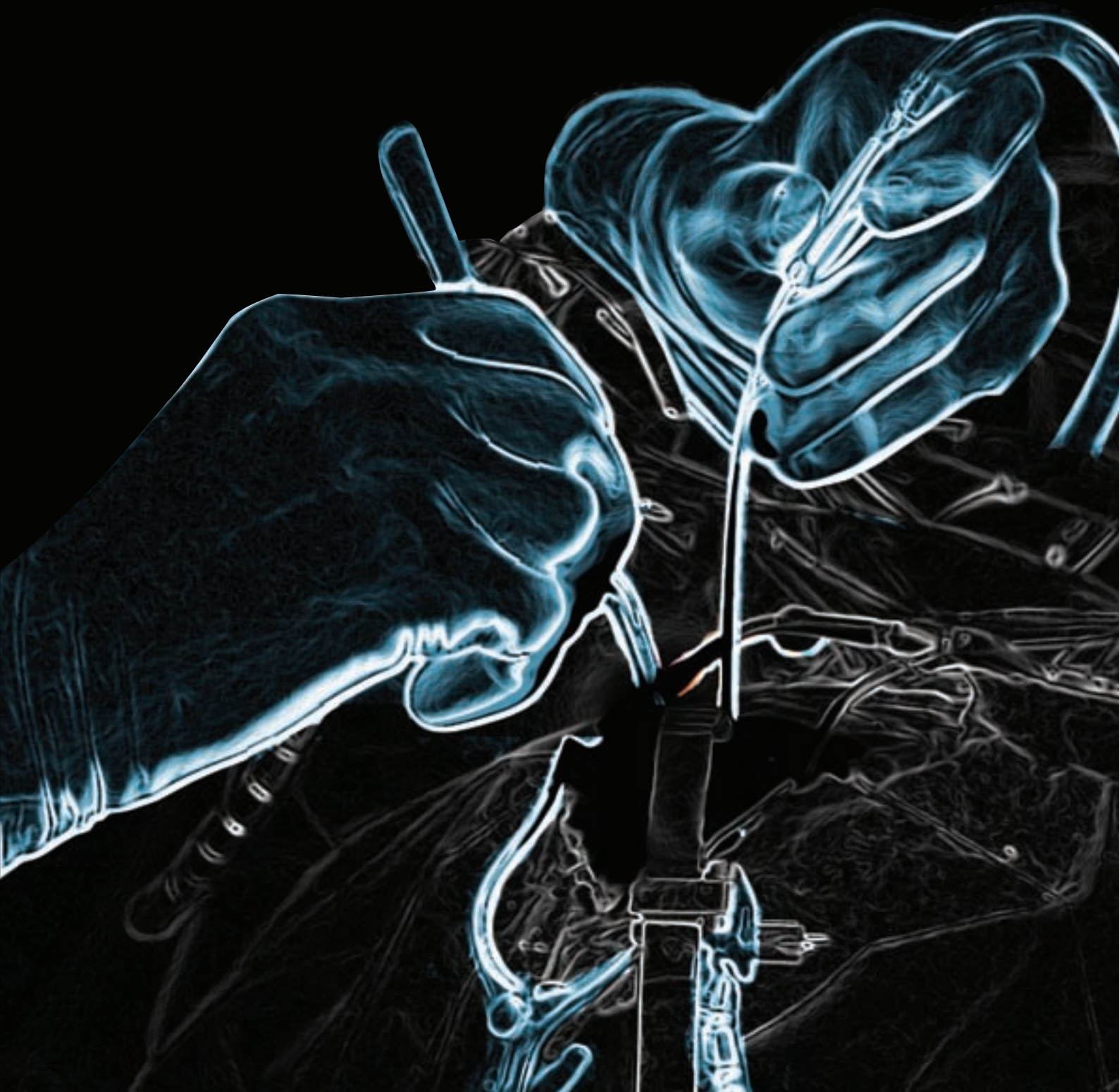
The Royal College of Surgeons of England

Surgical Research Report 2010-2011

Investing in research to improve patient welfare



Compiled by the Research Department at The Royal College of Surgeons of England
Photography by John Carr and Martyn Coomer
Edited by Jon Hackett
Produced by Adam Brownsell
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Research Department
The Royal College of Surgeons of England
35–43 Lincoln's Inn Fields
London
WC2A 3PE

CONTENTS

If surgery is to continue to develop it needs a vibrant research base and appropriate infrastructure. As this report makes clear, The Royal College of Surgeons of England plays a vital role in this essential component of the profession's activities. In 1993 College Council decided to close down its Hunterian Institute and invest the monies raised in the research fellowship scheme. This scheme has allowed many surgical trainees to learn the basics of research and has inculcated in them a lifelong passion for enquiry in their chosen surgical specialty. The reports outlined in this brochure bear witness to the impact that these fellowships and their associated projects are making on a variety of diseases and their treatment.

In addition to the fellowship scheme the Research Board makes travel grants available to selected trainees to allow them to visit centres abroad so as to learn and exchange ideas and develop professional friendships and contacts that often endure throughout their professional lives. The board also makes pump-priming awards to new consultants, allowing them to continue to develop their academic interests. These and other initiatives rely very much on the generosity of our donors to whom we are very grateful.

This support is vital for the health of surgical research, which in recent years has been severely affected by what many see as a flawed national medical research strategy. In 2007 only 1.4% of government spending on medical research was spent on surgery. This miserly amount becomes even starker when one considers that of the 12 million patients admitted annually to NHS hospitals in the UK, 35% are treated by surgical teams. It is high time that this discrepancy is reversed and the College Council and Research Board are determined to bring about the changes necessary.

Over the last decade or so medical research strategy has resulted in a concentration of effort into cell biology. Although this is a laudable pursuit, it has resulted in less investment into the physical sciences such as. physiology, electronics, physics applied to medicine, and engineering, so vital for surgical research. There have of course been some remarkable advances in cell biology, for instance stem cells and tissue engineering, but if such advances are to be translated into the clinic surgeons with the right background and training will be required. Never has this been more important and this realisation is gradually dawning on politicians.

It is of interest that the national medical research strategy has undergone a complete overhaul as a result of Sir David Cooksey's recent report. The Office for Strategic Coordination of Health Research has now been established as the overarching body that sets policy for both the Medical Research Council and the National Institute for Health Research (NIHR), with an emphasis on translation. In addition, the NIHR (that resulted from a clawing back of monies previously designated as service increment for teaching and research) is very much pushing an applied clinical research agenda under the dynamic leadership of Professor Dame Sally Davies. There are enormous opportunities for surgeons in this new landscape and the challenge is how best the College and its fellows and

CHAIRMAN'S INTRODUCTION

members can utilise the situation for the benefit of patients.

It is extremely heartening that at the final Council meeting of the 2008–2009 session members unanimously endorsed the need for the College to expand its role in research. All were agreed during this debate that the time was right to re-emphasise the College's determination to support its fellows and members to engage in research that is important for their patients. In order to do this we need a strategy that works for all the surgical community.

The development of this strategy has in fact been taking place for the last two years. Soundings have been taken throughout the profession as to how best to achieve the goals of promoting and developing surgical research and at the same time determining how research fits best into training. The latter is particularly important and to this end a seminar was held in November 2008 in conjunction with the Society of Academic and Research Surgeons (SARS) to debate the issue. A discussion document authored by the SARS Council has now been produced that is at present being circulated to all specialist associations. After appropriate modification it is hoped that this will be ratified by Council and will provide useful advice for trainees and trainers alike.

As part of strategy development it is essential to identify the problems and barriers and to develop solutions. The Research Board in conjunction with the Policy Unit held a seminar at the College in May 2009 to debate the issues. This was a high-profile affair, with the presence of some of the key decision-makers. Lord Darzi, the then Under Secretary of State for Health, Professor of Surgery and a Fellow of the College, gave up valuable time to be involved. His contribution was extremely important as were those from representatives of other key organisations such as the National Institute for Health and Clinical Excellence, and Cancer Research UK.

One theme to emerge was that the component of surgical research that explores innovative procedures requires a different approach to that which develops and tests new drugs. It is not always possible, either ethically or practically, to run a prospective randomised controlled trial of one surgical technique versus another. How for instance can a surgeon remain in equipoise when randomising a patient with an ultra-low rectal cancer to undergo a novel sphincter-saving technique or one which leaves him or her with a permanent stoma; indeed, how feasible would it be to obtain informed consent for such a trial?

It is clear that new measures of assessment for surgical techniques need to be developed and very importantly accepted as bona fide methods. The regulatory bodies and research councils need to be involved in this discussion so that unnecessary barriers do not get in the way of ensuring new techniques are tested and made available as quickly as possible. It is also necessary to get away from the ad hoc way in which new surgical interventions develop and importantly are disseminated. Safety must be a priority and surgeons must be seen to protect their patients. However, innovators

simultaneously need protection and support.

Integral to these concepts is training. For a surgical technique to be assessed fairly it needs to be taught appropriately. Training needs to go hand in hand with assessment. If the two are linked dissemination throughout a healthcare system becomes more efficient. To do all of this requires an infrastructure. The College has a very active Clinical Effectiveness Unit that also comes under the umbrella of the Research Board. It has been very successful in gaining grants for major audits of a variety of surgical procedures. However, more needs to be done.

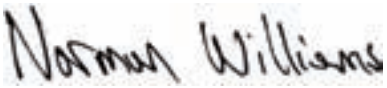
Trials units across the country and in different specialties need to develop the expertise to design the surgical trials that matter. Surgeons need to develop a mindset that demands from themselves and their colleagues evidence that what they do is effective. Putting patients into sound clinical trials needs to be the norm not the exception. The profession should grasp the initiative. Everyone can and should be involved; it should be realised that this type of activity is not just the responsibility of academic departments of surgery. The latter should certainly lead but they will require much wider support.

In order for such departments to take a leadership role they will need to be strengthened. Academic departments have over the last decade or so been severely depleted because of the abovementioned national research agenda. It is now time to resurrect them since there is a need to increase academic capacity. It is a scandal that between 2000 and 2007 there was a decrease in surgical academic lecturers by 50 %. With this in mind, pressure from the Research Board has been exerted at the highest level to change policy and there is an inkling that these protestations are at last having an effect. Time will tell whether supportive words will translate into action.

One legacy that Lord Darzi has left from his time in government is to convince the NHS that without innovation it will not develop and that innovation will in fact save money. He has made SHAs responsible for ensuring that they stimulate innovation in their provider trusts by this being a criterion for commissioning. Significant sums are available. In addition there are now prizes for innovation that rival in financial terms alone those of most of the prestigious international medical research awards. These are powerful incentives and surgeons, being extremely innovative, should benefit.

However, for surgery to grasp the opportunities that are now available via the national agenda it must be seen to help itself as well as to organise its research agenda appropriately. It has thus been mooted that the College engage in a major fundraising effort to generate funds that will allow its fellows and members to engage in the type of research that they feel is most appropriate for their patients. By doing so we will be in a strong position to influence national policy as well as to provide opportunities for cutting edge advances.

There is much to be done in the coming months and I would like to thank all those who have contributed so far, particularly to members of the Research Board who give of their time unreservedly. My thanks also to Martyn Coomer and his support staff whose considerable efforts ensure there are sufficient funds available to support present activities. Finally I would like to pay tribute to all those trainees who have competed for our fellowships. It is clear that there is a great appetite for research within the surgical community. If as is hoped our major initiative in fundraising is approved and is successful we will in future years be in a position to support many more deserving ideas.



Professor Norman S Williams
Chairman, Research and Academic Board

GALLERY

HARRY MORTON FELLOWS

Paul Lee with his supervisor Professor Alan Gross at the Mount Sinai Hospital, Toronto, Canada

Owase Jeelani with supervisor Professor James Rutka at the Hospital for Sick Children, Toronto

Dr Odeh Odeh with Professor Andrea Doria, director of medical imaging, the Hospital for Sick Children, Toronto

John Black explaining the implications of the EWTD to Edwina Hart, minister for health and social services, Welsh Assembly Government.

Professor Nick Cheshire and Jeremy Crane with visiting pupils from Northbridge House

Dr Jorunn Skattum teaching knot-tying to trainee on skills course in the Department of Health and Medical Services, Dubai

AN EVENING PROMOTING SURGERY FOR SIXTH-FORMERS HOSTED BY MANCHESTER LITERARY AND PHILOSOPHY SOCIETY

RUNNING A SKILLS COURSE IN AMMAN, JORDAN

SARS ANNUAL MEETING IN BRISTOL

Linda da Cossart and Brian Rees at Malcolm Puntis's lecture in Neath after a meeting of the Welsh Board

John Black talking to surgical staff at Graigravon hospital, Northern Ireland

Research fellows gathering to talk to freemasons in Shrewsbury

Peter Braithwaite and Asal Izzidien at the Welsh Surgical Society, Pembrokeshire

Professor Tony Narula on a visit to The Royal Marines Reserve, Tyne, Newcastle with Warrant Officer Screwy Driver and Lieutenant Colonel Phil Sanson

Allen Hogan, the President and Sir Leonard Fenwick touring the laparoscopic facilities at the Freeman Hospital, Newcastle

Anna Galeski, Dame Sue Street and Sir Bernard Ribeiro with Stefan Galeski research fellows

Sir Peter Simpson, John Smith and Bill Thomas meeting about the education review

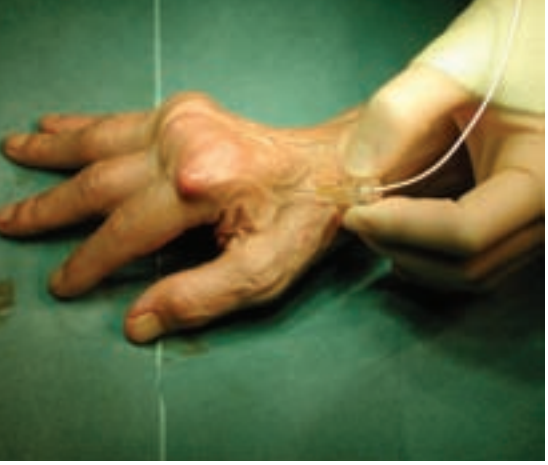
Professor Jim Neilson, dean of training, NIHR, addressing the research board

Professor Ashley Blom and the College team presenting to the freemasons in Bristol

Professor Chris Lavy with staff from the Kings School, Worcester

Brigadier Chris Parker and John Black visiting the Royal Centre for Defence Medicine in Birmingham

RESEARCH FELLOWS REPORTS



The interplay between hypoxia, angiogenesis and inflammation in rheumatoid hand disease

Rheumatoid arthritis affects 1–3% of the population worldwide and in over 60% of cases the hands are affected. This research paves the way for novel treatment that could slow down or halt the disease progression and help patients who have involvement of their hands.

Rheumatoid arthritis (RA) is a painful disease that causes progressive destruction of the joints and tendons of the hand. Painful reconstructive surgery is the only treatment available to improve hand function once the disease is established.

In RA the membrane covering the tendons is diseased. It becomes inflamed and invades the tendons making them weak and prone to rupture. This results in the typical hand deformities of RA and loss of hand function. There is good evidence that low oxygen levels (hypoxia) in the tissues are responsible for the inflammation that results in the tendon disease.

RA and non-RA patients undergoing elective hand surgery were recruited into the study. Oxygen measurements were taken from their hand and forearm musculature while under general anaesthesia. The surgery was performed as per norm and tissue samples were collected for laboratory experiments.

This study has shown that rheumatoid patients' hand and forearm musculature has a lower oxygen level than normal patients.

Furthermore the low oxygen has been shown to be responsible for producing higher amounts of enzymes that may be causing tendon rupture in rheumatoid patients. We anticipate that this new knowledge will enable us thereafter to design new treatments specifically targeted to preventing the development of the hand deformity.

Fig 1 Measurement of oxygen being taken from the hand of a patient. A gold electrode being used to measure oxygen levels while the patient is under general anaesthesia

Fig 2 Preoperative planning: Mr Kang (right) and Mo in the operating room going through the medical notes of the next patient who will be involved in the research

MR MO AKHAVANI

Fellowship/sponsor
Joint College/Dunhill Medical Trust Research Fellowship

Supervisor
Mr Norbert Kang and Dr Ewa Paleolog

Site of work
The RAFT Institute of Plastic Surgery and the Kennedy Institute of Rheumatology

Publications

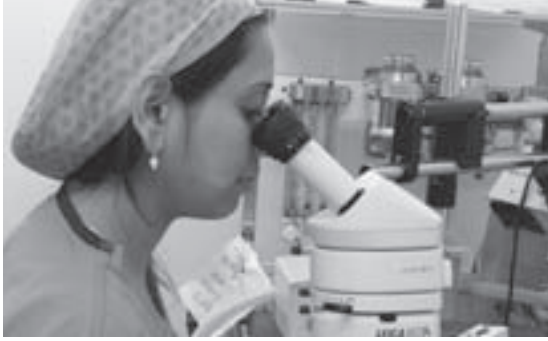
- Sivakumar B, Akhavani MA, Winlove CP *et al.* Synovial hypoxia as a cause of tendon rupture in rheumatoid arthritis. *J Hand Surg Am* 2008; **33**: 49–58

- Akhavani MA, Paleolog E, Kang N. The role of hypoxia in rheumatoid hand disease. *Journal of Hand Surgery:* European Volume 2007; **32 (Suppl 1):** 99

Presentations

- *Hypoxia Upregulates Angiogenic Properties of Rheumatoid Synovial Cells.* European Association of Plastic Surgeons, Madeira, Portugal, May 2008

- *Tenosynovial Angiogenesis in Rheumatoid Hand Disease*. British Society for Surgery of the Hand, Leicester, Spring Meeting 2008



In vivo tissue integration of tendon progenitor construct: a model for new cell-based tissue therapy

Treatment for tendon injury and disease is usually surgical and followed by prolonged rehabilitation. With 600,000 tendon or ligament injuries every year this results in a £25 billion loss by the UK trade industry every year.

Grafts are free pieces of tissue that are used to replace lost or damaged tissue. The aim of this research is to understand better the role of host and graft cells in graft healing. The practice of reconstructive surgery is reliant upon use of grafted or transplanted material. Tendons act as a good model to study grafting biology as it has a relatively simplistic organisation that allows events to be followed with great precision. Though a substantial amount of research has been carried out no clear conclusion has yet been reached as to how tissue grafts are integrated into the host environment.

An animal model that expresses green fluorescent protein in all its cells was used for the study. In the first phase of the project a piece of tendon was removed from the donor animal and placed into the host animal. The graft and surrounding areas were then investigated using a wide variety of techniques. Results show that graft cells are present at three days and three weeks but disappear by three months, suggesting cellular repopulation of the graft between the three weeks and three months period.

In the second phase of the project we are investigating a novel artificial tendon, which has shown properties similar to fetal tendons that show scarless healing (regeneration). Tissue engineering is emerging as the surgical therapy of the future. Engineering of tendons has so far proved to be unsatisfactory due to lack of mechanical strength, which has lagged greatly behind normal tendon.

The implications of an engineered tendon could have a major impact in hand and sport-related injuries as well as various diseases that affect the musculoskeletal system, ie rheumatoid arthritis. An off-the-shelf tendon construct may significantly reduce donor site problems and improve recovery time after tendon surgery if it were to have better and faster healing properties. It therefore has the potential to reduce disability in millions of people suffering from musculoskeletal diseases.

MISS NAWSHEEN ALAM

Fellowship/sponsor
Blond McIndoe Research Fellowship

Supervisor
Mr Jason Wong and Professor DA McGrouther

Site of work
University of Manchester

Publications

- Alam NH, Jason JW, McGrouther DA. A Novel Model for the Investigation of the Fate of Tendon Grafts. TERMIS-EU Meeting Abstracts London, UK September 4–7, 2007. *Tissue Eng 2007*; 13: 1,633–1,778

Presentations

- *Fate of tendon grafting using transgenic animal.* Oral presentation at British Association of Plastic, Reconstructive and Aesthetic Surgeons meeting, July 2009
- *A Novel Model for the Investigation of the Fate of Tendon Grafts.* Poster presentation at Tissue Engineering and Regenerative Medicine Internal Society meeting 2007

Prizes

- Award for best poster presentation at Faculty of Medicine, University of Manchester poster presentation day, 15 January 2009
- College/British Society for Surgery of the Hand Fellowship in Hand Surgery 2007–2008

Fig 1 Nawsheen carrying out tendon surgery with the help of an operative microscope
Fig 2 Nawsheen cutting sections of samples, supervised by Dr Jason Wong

The epidemiology and management of acute urinary retention

The overall mortality of acute urinary retention is very high – almost one in five men died within one year.

Acute urinary retention (AUR) is characterised by the sudden and painful inability to pass urine. It causes significant morbidity, frequently results in emergency hospital admission and often requires surgery. However, the prognostic significance of AUR in men has been inadequately described. Furthermore, a number of novel treatments have been developed and introduced into clinical practice without thorough evaluation. With this in mind, the overall aims of this research were to investigate the mortality of men after AUR and to consider their treatment options.

We extracted data from the Hospital Episode Statistics database, an administrative database of all admissions to NHS hospitals in England. We found that the overall mortality of AUR is very high – almost one in five men died within one year. Mortality rates were higher in older men and in those with additional coexisting diseases (comorbidity). Through identifying and treating comorbidity it is hoped that the high mortality of these patients may be reduced.

One of the minimally invasive treatments for a man with AUR is to insert a stent (supportive metal tube) into the prostate that will allow him to pass urine again. We systematically reviewed the research evidence for the two commonest types of prostate stent in current clinical use.

We found that although they are effective at treating AUR, a paucity of long-term follow-up data means that their use should be restricted to frail and elderly men.

This research builds on the work of the Clinical Effectiveness Unit of The Royal College of Surgeons of England and further supports the use of administrative data for evaluating health care outcomes. As part of this research project an algorithm was developed that may improve the identification of comorbidity and enhance the reliability of future research that uses administrative data.

Fig 1 Jim operating on a patient who had experienced acute urinary retention
Fig2 Jim teaching surgical skills in Ghana

MR JIM ARMITAGE

Fellowship/sponsor
Joint College/Dunhill Medical Trust Research Fellowship

Supervisor
Professor Jan van der Meulen and Mr Mark Emberton

Site of work
Clinical Effectiveness Unit, The Royal College of Surgeons of England

Publications

- Armitage JN, Sibanda N, Cathcart PJ *et al.* Mortality in men admitted to hospital with acute urinary retention: database analysis. *BMJ 2007:* **335**: 1,199–1,202

- Armitage JN, Cathcart PJ, Rashidian A *et al.* Epithelializing stent for benign prostatic hyperplasia: a systematic review of the literature. *J Urol 2007;* **177**: 1,619–24

Presentations

- Armitage JN, Sibanda N, Cathcart PJ *et al. Acute urinary retention is associated with an increased risk of mortality.* BAUS, Glasgow 2007

- Armitage JN on behalf of the College Comorbidity Consensus Group. *An updated and validated approach to identify comorbidity in ICD-10 administrative data.* Society of Academic and Research Surgery/section of academic urology meeting, Bristol, 2009

The role of tumour suppressor genes in renal cancer

MR RAVI BAROD

Fellowship/sponsor
Joint College/Kidney Research UK Research Fellowship

Supervisor
Tim O'Brien and Patrick Maxwell

Site of work
University College London, Imperial College London and Guy's and St Thomas' NHS Foundation

Publications

- Harten SK, Shukla D, Barod R *et al.* Regulation of renal epithelial tight junctions by the von Hippel-Lindau tumor suppressor gene involves occluding and claudin 1 and is independent of E-cadherin. *Mol Biol Cell* 2009; **20**: 1,089–1,101
- Tuthill M, Barod R, Pyle L *et al.* A report of succinate dehydrogenase B deficiency associated with metastatic papillary renal cell carcinoma: successful treatment with the multi-targeted tyrosine kinase inhibitor sunitinib. *BMJ Case Reports* 2009 [doi:10.1136/bcr.08.2008.0732]

Presentations

- American Urological Association, Chicago, USA 2009 (best poster in session)
- European Association of Urology, Stockholm, Sweden 2009 (best poster in session)

Prizes

- Royal Society of Medicine, section of urology, short papers prize 2006 and Geoffrey Chisholm Prize 2009
- British Association of Urological Surgeons, section of academic urology/Society of Academic and Research Surgeons prize for best clinical presentation 2009

Advanced kidney cancer is currently incurable and kills 4,000 people in the UK each year.

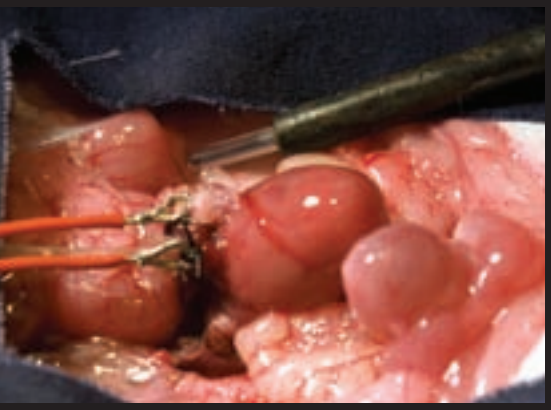
As a urologist I look after patients with kidney cancer, which affects 7,000 people a year in the UK. Early disease is usually cured by surgery but one-third of patients present with advanced disease that is currently incurable. My research involves the cellular biology of kidney cancer and specifically a tumour suppressor gene called phosphatase and tensin homolog (PTEN). I collected tissue from 42 patients with kidney cancer and found that a subset of patients had mutations in PTEN. I then comprehensively investigated the functions of PTEN and the consequences of mutation of this gene.

I made four key findings. First, that PTEN regulates levels of vascular endothelial growth factor (VEGF), a factor that stimulates formation of blood vessels in the tumour. Second, that PTEN regulates migration of kidney cancer cells so mutation in PTEN allows them to disperse and spread. Third, PTEN normally controls growth of kidney cancer cells so when PTEN is mutated growth becomes uncontrollable. Finally and most significantly, tumour growth is suppressed by functional PTEN in animal models.

These tantalising findings have shown that mutation in PTEN can contribute to the tumour characteristics of kidney cancer and may be one of several steps that a normal kidney cell takes on its path to becoming a cancer cell. This knowledge may be exploited in the development of new targeted therapies, with the aim of improving survival of patients with advanced kidney cancer. Indeed, since starting this project, two new drugs (temsirolimus and everolimus) that act on downstream effectors of PTEN have been licensed for use in advanced kidney cancer.

My research may also provide a means of understanding which patients will respond to such therapies by identifying tumours with mutations in PTEN. This could lead to individualised therapeutic programmes that prevent unnecessary treatment of non-responders, thereby decreasing toxic effects and increasing cost-effectiveness of these expensive drugs. Collectively my findings may be synthesised into the rapidly increasing knowledge of the biology of kidney cancer, with the overall aim of improving patient survival and potentially curing this disease in the future.

Fig 1 Annual meeting of the Provincial Grand Lodge of Somerset, Weston Super Mare, 3 April 2009



Sildenafil augments myocardial protection in cardiac transplantation

Despite advances in our understanding of how the heart is injured during transplantation, nearly one in ten patients dies as a result of graft failure following this procedure.

Heart failure causes severe debilitation due to breathlessness with even the slightest activity and affects an increasing number in developed countries. Heart transplantation not only prolongs the survival of these patients but also allows them to resume a near-normal activity level. Protection of the heart during transplantation remains suboptimal; around 10 % of patients die within the first 30 days of the procedure. Sildenafil citrate is a drug originally developed for heart disease, now most commonly used to treat erectile dysfunction. It has been shown in the laboratory to have a profound protective effect on the heart. During heart transplantation, and to a lesser extent all forms of open heart surgery, the blood supply to the heart is interrupted, causing ischaemic injury. This is limited in clinical practice by the administration of a preservation solution and cooling the heart. The aim of our study was to investigate whether the protective effects of sildenafil could be used to improve the protection afforded by current methods.

We developed a new laboratory model of heart transplantation in the rodent and used this to investigate the protective effects of sildenafil. We found that in a clinically applicable dose, sildenafil significantly improved several aspects of the function of the transplanted heart if administered to the donor shortly before transplantation. We have also made significant strides toward understanding the molecular mechanisms involved in the protection afforded by sildenafil, identifying key enzymes and cellular targets involved. Further work will investigate the effect that sildenafil given to the donor will have on the other transplanted organs, with some early laboratory work suggesting that it may also improve the outcome in lung transplantation.
The use of sildenafil in cardiac surgery is also currently under investigation in an international multi-centre clinical trial in patients undergoing heart valve surgery and mechanical heart implantation.

Fig 1 Phil discusses results with his supervisors
Fig 2 A rodent heart shortly after transplantation
Fig 3 Phil presenting his work to the Shears family

MR PHIL BOTHA

Fellowship/sponsor
Shears Northern Surgical Research Fellowship

Supervisor
Professor JH Dark and Dr GA MacGowan

Site of work
Institute of Cellular Medicine, Newcastle University

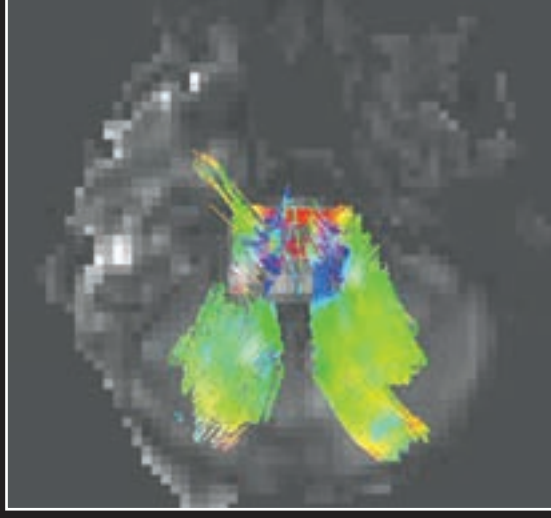
Publications

- *Am J Physiol Heart Circ Physiol*, under review
- *J Heart lung Transplant*, in press

Presentations

- International Society for Heart & Lung Transplantation, annual scientific meeting, Boston, USA, April 2008
- International Society for Heart & Lung Transplantation, annual scientific meeting, San Francisco, USA, May 2007

Diffusion MRI and tractography in the evaluation of and surgical planning for paediatric central nervous system (CNS) tumours



MR JONATHAN BULL

Fellowship/sponsor
Harold Bridges Research Fellowship

Supervisor
Dr CA Clark

Site of work
RCS Unit of Biophysics, UCL Institute of Child Health

Paediatric CNS tumours require invasive biopsy to determine the diagnosis. The extent of surgical resection is the greatest determinant of survival.

The aim of the project was the evaluation of the utility of diffusion magnetic resonance imaging (MRI) in radiological discrimination of tumours and subsequently, the creation of images of white matter connections (tracts) between areas of the brain. The intention was to validate the tractography images through linking tract disruption with presence of neurological deficits associated with those anatomical connections.

Diffusion MRI is a technique that uses the distortion of the normal random movement of water by the presence of tissues to demonstrate the tissue structure. This is also under evaluation in the adult population and my work builds on this. Data were collected using a specific MR sequence and were analysed through computer algorithms and compared to the findings of clinical examinations.

Discrimination of paediatric tumour types on purely radiological grounds was attempted. The intention was to obviate the need for surgical biopsy for accurate diagnosis. This would remove the associated risks of injury and mortality and greatly reduce the stress to the children and their families. Extended analysis of the base data allowed production of images of relevant white matter tracts, the integrity of which, visually represented, was hypothesised to correlate with structural destruction or displacement of the connections in vivo. This would hence be associated with evidence of neurological deficits evaluated by clinical examination.

Diffusion data, statistically analysed, allowed discrimination of several types of paediatric tumours. The number of groups discriminated were greater than previous research had achieved, particularly for rarer, more aggressive tumours in which biopsy would be the likely surgical option. Tractography in tumour patients revealed an association between the integrity of the tract and the presence of clinical neurological deficits.

These findings are novel in the paediatric population and work continues in this field at the Institute of Child Health. The intention is to combine radiological investigations to obviate the need for surgical biopsy for diagnosis and treatment. Preoperative diagnosis and planning, through functionally validated tractography, facilitates more aggressive, safer resections. In paediatric central nervous system tumours, the extent of resection is the greatest determinant of survival.

Publications

- Bull JG, King M, Saunders D, Clark CA. The use of apparent diffusion coefficient histograms in the discrimination of paediatric CNS tumours (submitted to *Radiology*)

Presentations

- Bull J, King M, Clark CA. *Use of ADC parameters for discrimination of paediatric posterior fossa tumour.* International Society for Magnetic Resonance in Medicine conference, Toronto, Canada, May 2008
- Bull J, King M, Saunders D *et al. Tractography of Cerebellar Pedunclar volume in Posterior fossa tumours.* International Society for Paediatric Neurosurgery conference, Liverpool, September 2007

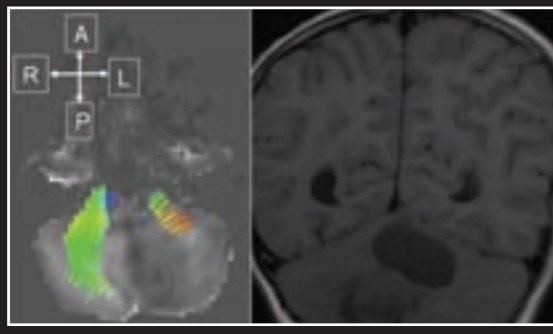


Fig 1 Normal cerebellar tractograpy anatomy
Fig 2 Patient JA, tractography and MRI. Left cerebellar clinical signs, diminished left cerebellar peduncle tract volume, primarily midline and left-sided lesion

The use of radiosensitising agents in the treatment of muscle-invasive bladder cancer

MISS ALEX COLQUHOUN

Fellowship/sponsor
Joint College/Cancer Research UK Research Fellowship

Supervisor
Professor JK Mellon

Site of work
Leicester General Hospital

Publications

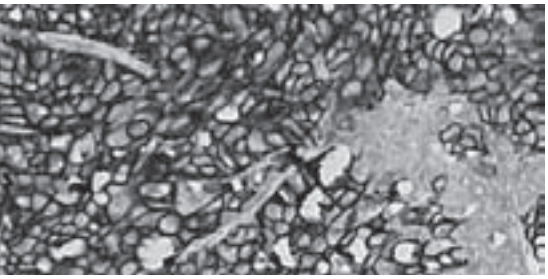
- Colquhoun AJ, Sundar S, Rajjayabun PH *et al*. Epidermal growth factor receptor status predicts local response to radical radiotherapy in muscle-invasive bladder cancer. *Clin Oncol (R Coll Radiol)* 2006; **18**: 702–9

- Colquhoun AJ, Mchugh LA, Tulchinsky E *et al*. Combination treatment with ionising radiation and gefitinib ('Iressa', ZD1839), an epidermal growth factor receptor (EGFR) inhibitor, significantly inhibits bladder cancer cell growth in vitro and in vivo. *J Radiat Res (Tokyo)* 2007; **48**: 351–360

Presentations

- *Epidermal growth factor receptor (EGFR) status predicts outcome following external beam radiation therapy for muscle-invasive bladder cancer*. European Assocation of Urology, Vienna, Austria, 2004

- *Epidermal growth factor receptor (EGFR) blockade with erlotinib potentiates the antitumour effect of ionising radiation in bladder cancer cell lines*. American Urological Association, San Francisco, USA, 2004



The use of epidermal growth factor receptor inhibitors significantly enhances the effectiveness of radiotherapy on bladder cancer cells both in vitro and in vivo.

Bladder cancers that penetrate the muscular wall of the bladder (invasive bladder cancer) carry a poor prognosis, with survival rates following treatment (radical surgery or radical radiotherapy) in the region of 50%. Epidermal growth factor receptor (EGFR) is a receptor expressed by a high proportion of cancers. Previous work has shown EGFR is commonly expressed in invasive bladder tumours. Other authors have shown that radiotherapy can activate EGFR, causing cancer cells to proliferate, and this may be an underlying cause of resistance to this mode of cancer treatment.

We undertook a study to determine whether the EGFR status of a series of invasive human bladder tumours related to outcome following treatment with radical radiotherapy. We also performed a series of in vitro and in vivo experiments to assess whether radiotherapy activated EGFR in bladder cancer cell lines. Subsequently we assessed the ability of two treatments known to inhibit the activation of EGFR, gefitinib and erlotinib, at enhancing the effectiveness of radiotherapy in bladder cancer cells.

Using immunohistochemistry we assessed the EGFR status of the 110 bladder tumours from patients who subsequently received treatment for invasive bladder cancer with radical radiotherapy. 72% of tumours assessed expressed EGFR (see Figure 1). Patients whose tumours were EGFR-negative exhibited a significantly improved initial response to treatment with radiotherapy (p=0.05). However, negative EGFR status was not an independent prognostic factor for improved overall survival following treatment with radiotherapy.

In vitro experiments using Western blotting confirmed the ability of radiotherapy to activate EGFR in bladder cancer cells (see Figure 2). Pre-treatment of cells with anti-EGFR treatment, either gefitinib or erlotinib, inhibited this activation. Subsequent in vitro and in vivo experiments using clonogenic assays confirmed combining gefitinib with radiotherapy significantly inhibited bladder cancer cell growth compared to treatment with either monotherapy alone. Taken as a whole these results provide a basis for undertaking a clinical trial to assess the efficacy of anti-EGFR treatments in enhancing the effectiveness of radical radiotherapy in patients with invasive bladder cancer.

Fig 1 Irradiator set-up for treatment of bladder cancer cells with radiotherapy
Fig 2 Invasive bladder cancer tissue staining positively for epidermal growth factor receptor (dark brown area)

The effect of intervention on balance in older patients with claudication

Overall, over 40% of claudicants demonstrate objective evidence of abnormal balance. A supervised exercise programme aimed at at-risk claudicants may improve balance and potentially reduce the risk of falling.

Falling and allied balance deficiencies are common, associated with injury and reduced independence among the elderly. Intermittent claudication is a condition that presents with cramp-like pains in the muscle compartments of the legs, brought on by walking and relieved by rest, and is due to poor blood flow to the muscles. It is a common problem in the elderly and is linked with poor physical function and impaired quality of life. Previous studies suggest that claudicants are at risk of balance deficiencies and as such, identification of patients with impaired balance allows preventative measures to be adopted to reduce falls risk, which is of enormous public health importance.

We objectively assessed balance deficiencies using standard clinical objective measures of physical function and computerised dynamic tests performed on a controllable platform under dynamic test conditions. This technique measures patient's body sway relative to the maximum limits of stability under six different sensory conflict conditions. Quality of life and an objective assessment of fear of falling was also assessed. The role of standard treatment regimes was assessed.

Overall 40 % of claudicants demonstrated abnormal balance. This was as a result of a combination of vestibular, sensory and visual dysfunction. Furthermore, claudicants with abnormal balance were more likely to have a history of falls but did not show increased fear of falling, thus potentially rendering these patients at greater risk of falling due to overconfidence or reduced awareness of hazards. Solely improving the blood supply to the legs of claudicants by balloon angioplasty does not seem to improve balance but a standard supervised exercise programme targeted at claudicants with poor balance may produce improvements.

Work continues to identify potential reasons for the observed balance deficiencies and ways of adapting the supervised exercise programme to improve results.

MR PADDY COUGHLIN

Fellowship/sponsor
Joint College/Dunhill Medical Trust Research Fellowship

Supervisor
Mr Ian Chetter

Site of work
Academic vascular unit, Hull Royal Infirmary

Presentations

- 44th Congress of the European Society for Surgical Research, Nîmes, France, 2009
- International Society of Biomechanics, Cape Town, 2009

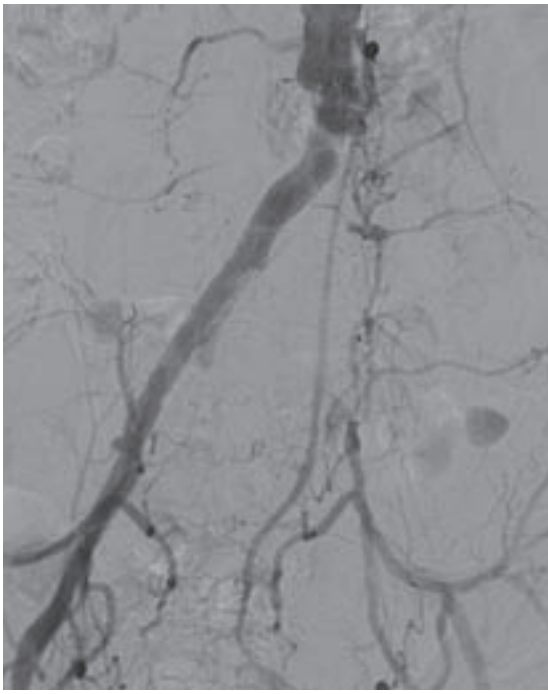
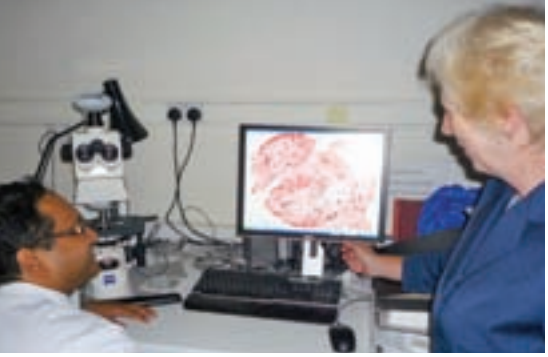


Fig 1 Patrick examining a patient on the ward after an angioplasty
Fig 2 Angiogram of a patient prior to and following balloon angioplasty



Cholinergic signalling pathways in the superficial layers of the human bladder; comparing health, disease and the effect of botulinum toxin type A

MR SOUMENDRA NATH DATTA

Fellowship/sponsor
With support from the Rosetrees Trust

Supervisor
Professor Clare J Fowler and Dr Apostolos Apostolidis

Site of work
UCL Institute of Neurology

Publications

- Roosen A, Datta SN, Chowdhury RA et al. Suburothelial myofibroblasts in the human overactive bladder and the effect of botulinum neurotoxin type A treatment. *Eur Urol* 2009; **55:** 1,440–8 Epub Nov 18
- Datta SN, Roosen A, Pullen A *et al.* Cholinergic pathways in the superficial bladder layers in human detrusor overactivity and changes with Botulinum Neurotoxin type A (BoNT/A) (in press)

Presentations

- American Urological Association (AUA) meeting, Chicago, USA, May 2009
- European Association of Urology annual meeting, Milan, Italy, March 2008

Prizes

- Best of AUA prize, Incontinence, AUA meeting, Chicago, May 2009
- Best scientific presentation, bladder dysfunction session, European Association of Urology annual meeting, Milan, March 2008

One in eight people develop an overactive bladder, with problems ranging from incontinence, social isolation and the need to wear pads.

Bladder sensation is poorly understood. An overactive bladder is a common condition affecting up to one in eight individuals and can result in uncontrolled leakage of urine. It is thought that neurotransmitters close to the surface of the bladder are involved in an overactive bladder. Our study looked at the use of botulinum toxin as a treatment of 36 patients with overactive bladders, in comparison to nine healthy individuals.

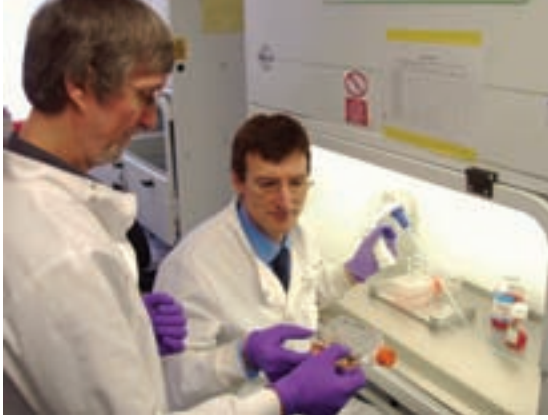
Our study involved the microscopic examination of tissue from bladder walls and the observation of changes in neurotransmitter receptor levels within these tissues. We found decreased receptor levels in patients with overactive bladders compared to healthy subjects. After treatment with botulinum toxin, these receptors went back to expected normal levels. These patients reported dramatic improvements in their symptoms of needing to run to the toilet and leakage.

This research is based on the findings of successful treatment of patients with overactive bladder. Over the last few years there has been considerable interest in botulinum toxin and its therapeutic applications. Research is helping eventually to allow this treatment to be licensed for use. This is a long-term project, the results of which can be built upon by others to further study the long-term effects of this drug.

Quality of life is markedly affected by this condition and close to a third of patients report feeling depressed. The combination of urinary urgency and fear of incontinence often makes sufferers shy away from social situations and activities away from home. This treatment dramatically improves the quality of life of patients who were often housebound and required several pads a day. After successful treatment, patients demonstrate a new-found confidence in being able to participate in normal social activities without fear of embarrassment or the need to seek out toilets.

Fig 1 Analysing bladder tissue under the microscope
Fig 2 Prize-winning poster presentation at the American Urological Association 2009

Investigations into therapies for recurrent respiratory papillomatosis and human papillomavirus 6



MR ADAM DONNE

Fellowship/sponsor
College Research Fellowship

Supervisor
Mr Jarrod Homer, Dr Ian Hampson and Dr Lynne Hampson

Site of work
St Mary's Hospital, Manchester

There are no laboratory test systems upon which to trial drug therapies for recurrent respiratory papillomatosis and no scientific evidence that the most contemporary treatment (cidofovir) is effective against the causative agents (HPV 6/11) of this condition.

Recurrent respiratory papillomatosis (RRP) is a condition in which warty growths (benign tumours) grow within the voice box and airway, hence impairing breathing. Patients require repeated surgical removal to keep the airway clear as once removed the tumours regrow. There is no cure. The most contemporary treatment is a drug called cidofovir which is injected directly into the tumours. Cidofovir incorporates into DNA and prevents regrowth. The effectiveness of cidofovir has never been evaluated scientifically against the main cause of RRP, namely human papillomavirus (HPV 6 and 11). The work was planned to generate objective laboratory test systems and address this issue.

Part of the HPV DNA was inserted into human cells in the laboratory to generate a novel cell-based test system. Non-HPV cell lines were also generated to act as objective comparators. The cell system was tested with increasing doses of cidofovir. At low concentrations of cidofovir the growth and survival rate of cells containing HPV DNA increased beyond that of non-HPV cells.

This identified the relatively non-specific nature of cidofovir for treating RRP. The improved survival of HPV DNA containing cells supported the clinical observation of increased growth of RRP tissue in patients if the interval between cidofovir injections was too long.

Further studies demonstrated that cidofovir exposure induced the HPV DNA containing cells to increase the expression of genes known to be associated with numerous cancers. This indicated that cidofovir may increase the risk of cancer formation in RRP patients. Indeed, cidofovir is already known to cause cancer in rat studies. This work therefore raises serious concerns.

This research continues and now focuses on the evaluation of potential biomarkers using RRP patient biopsies. Work may identify the patients who will benefit from cidofovir without risk of cancer formation and those who may not, hence preventing unnecessary exposure.

Publications

- Donne AJ, Hampson L, He XT *et al*. Cidofovir induces an increase in levels of low-risk and high-risk HPV E6. *Head Neck* 2009; **31**: 893–901
- Donne AJ, Hampson L, He XT *et al*. Effects of cidofovir on a novel cell-based test system for recurrent respiratory papillomatosis. *Head Neck* 2007; **29**: 741–750

Presentations

- 10th International Congress of the European Society of Pediatric Otorhinolaryngology, ESPO. Budapest, June 2008
- British Association of Paediatric Otolaryngology, September 2007

Prizes

- Suzanna Leighton Fellowship prize 2007
- Astra/Zeneca Surgical Trainees' prize 2007

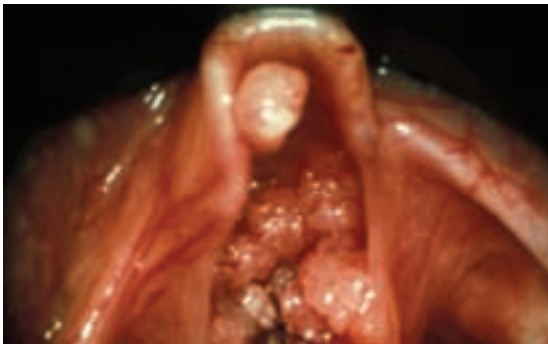
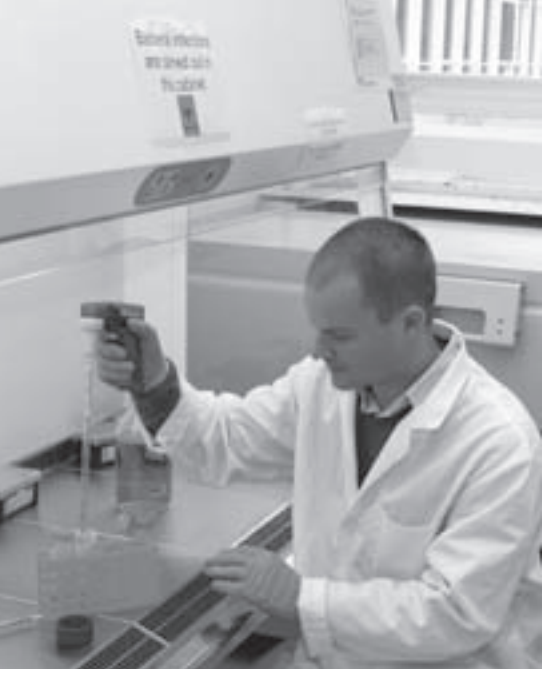


Fig 1 Adam performing cell culture experiment with advice from supervisor Dr I N Hampson
Fig 2 Endoscopic image of a larynx with severe respiratory papillomatosis



Effects of interactions between bacterial species in the human larynx on epithelial barrier function

Bacteria are everywhere. They colonise the whole of the external surface of the human body including the mouth, gut and the larynx.

They often cause no harm to their host but in the larynx they have been implicated in serious diseases such as laryngitis, supraglottitis, subglottic stenosis and even possibly laryngeal cancer. However, the study of the bacteria of the larynx has been neglected and never formally characterised using modern DNA-based techniques – the true gold standard. Our objective was to perform the first full analysis and identify species that may be implicated in these conditions.

Biopsies were taken from the larynx of 18 patients attending for routine ENT surgery. Bacterial DNA was extracted, which was used to perform the first full characterisation of the bacterial flora of the larynx ever undertaken. This yielded a far larger diversity of bacteria than ever previously identified as well as a variation between laryngeal subsites. We also identified an unusual lack of staphylococcal species in the larynx, which are often prevalent elsewhere in the nose and mouth.

We then studied the effect of common laryngeal bacterial species on preventing the adhesion and invasion of these staphylococcal species to the laryngeal mucosa using a laryngeal cell monolayer. We discovered that some of the common streptococcal species prevented staphylococcal invasion and hence may help to prevent staphylococcal infections in the larynx.

This work has provided a novel insight into the effects that interacting bacteria can have on the laryngeal flora, and has identified a number of areas for research to explore further these interactions and their effects on laryngeal disease.

Fig 1 Stuart and Tristan Cogan at work in the lab
Fig 2 Stuart with a patient

MR STUART GILLETT

Fellowship/sponsor
College Research Fellowship

Supervisor
Dr T Cogan and
Dr L Rees

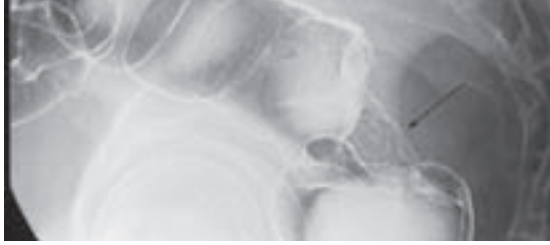
Site of work
Bristol University, Langford

Presentations

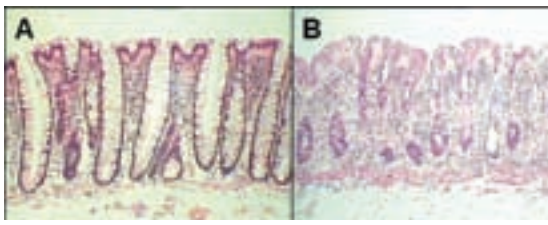
- European Laryngological Society, Barcelona, Spain, 2008
- Society of Academic and Research Surgery, Bristol, 2009

Prizes

- Royal Society of Medicine, laryngeal equipment grant, 2008



The role of the supramucosal defence barrier in determining the effects of pre-operative radiotherapy on normal tissue and tumours in patients with rectal cancer



Colorectal cancer is the third most common cancer in the UK after breast and lung and the second most common cause of cancer death, with around 36,000 new cases and 16,000 deaths per year.

Avoidance of local recurrence following surgery is an important goal in the treatment of rectal cancer as it causes severe symptoms, is difficult to treat and may result in death. Pre-operative radiotherapy decreases local recurrence rates, but may increase the risk of anastomotic leakage (failure of the join in the bowel to heal). This is a major complication (accounting for one-third of post-operative deaths), which may outweigh any potential benefit of radiotherapy.

Mucin (MUC) and trefoil (TFF) proteins have been shown to be key mediators of mucosal healing, while they become dysregulated in colorectal cancer and may influence tumour radiosensitivity. MUC2 is the major mucin expressed in the colorectum, where it is co-localised with TFF3, and their function may be dependent on their interaction. The purpose of this project was to investigate changes in the levels of these proteins following irradiation, which has not been studied previously.

Patients were asked to provide samples of tissue before and after radiotherapy, along with controls that underwent surgery alone. Samples were stained for MUC/TFF proteins using antibodies (immunohistochemistry) and computer-assisted image-analysis was used to assess levels of expression.

Unexpectedly, radiation damage was detected in normal tissue at the proximal resection margin (the cut end used to re-join the bowel), which had been assumed to lie outside the irradiated field. Furthermore, levels of MUC2 and TFF3 in normal tissue were significantly decreased following radiotherapy. These findings may lead to impaired colonic healing and an increased risk of anastomotic leakage following radiotherapy. Pre-treatment tumour levels of MUC5B correlated with tumour regression (response).

This project has shown that the effects of pre-operative radiotherapy may be more widespread than previously realised and that changes in the expression of key proteins can be detected in normal tissue. Ongoing research would need to confirm these preliminary findings, but measurement of MUC5B levels in pre-operative tumours may prove a promising 'marker' enabling radiotherapy to be targeted more effectively in the future.

Fig 1 Barium enema study showing a large rectal cancer

Fig 2 Normal colonic tissue from outside the intended irradiated field showing clear signs of radiation damage – reduced crypt height and number (B) compared with equivalent tissue in a non-irradiated patient (A)

MR DAMIAN GERARD GLANCY

Fellowship/sponsor
Enid Linder Foundation

Supervisor
Mr Michael Thomas

Site of work
Bristol Royal Infirmary

Publications

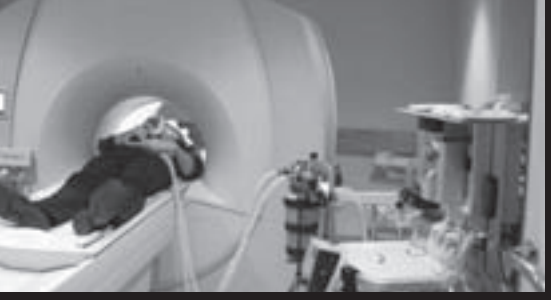
- Glancy DG, Corfield AP, Thomas MG. Expression Of Muc2 In Normal Colonic Mucosa Is Decreased Following Pre-operative Radiotherapy For Rectal Cancer: Implications For Anastomotic Healing. *Colorectal Disease 2008;* **10 (Suppl 1)**: 25

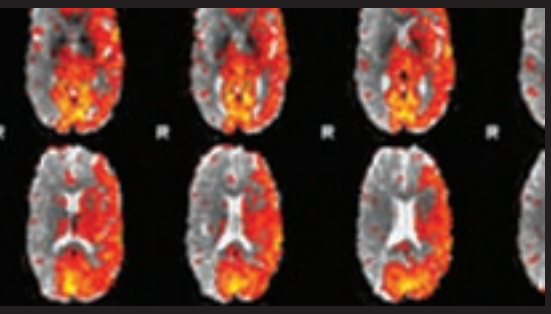
- Glancy DG, Thomas AP, Radburn-Smith MA, Thomas MG. Tissue Damage Is Detectable At The Proximal Resection Margin Following Pre-operative Radiotherapy For Rectal Cancer: Implications For Anastomotic Healing. *Colorectal Disease* 2008; **10 (S1)**: 26

Presentations

- *Expression Of Muc2 In Normal Colonic Mucosa Is Decreased Following Pre-operative Radiotherapy For Rectal Cancer: Implications For Anastomotic Healing.* Association of Coloproctology of Great Britain and Ireland annual meeting 2008, International Convention Centre, Birmingham

- *BAG-1 expression in human rectal cancer and the effect of neo-adjuvant radiotherapy.* British Society of Gastroenterology annual meeting 2005, International Convention Centre, Birmingham





Mapping of cerebral haemodynamics in carotid disease using advanced MRI techniques

Patients with impaired brain blood flow reserve had a significantly increased number of recurrent mini-strokes. Following carotid surgery patients had a significant improvement in the brain blood flow reserve.

MR STEPHEN D GOODE

Fellowship/sponsor
Grand Lodge 250th Anniversary Fund

Supervisor
Professor D Auer and Mr S MacSweeney

Site of work
Department of Academic Radiology, University of Nottingham; iointly with Department of Vascular and Endovascular Surgery, Queens Medical Centre, Nottingham

Publications

- Goode SD, Krishan S, Alexakis C *et al.* Precision of cerebrovascular reactivity assessment with use of different quantification methods for hypercapnia functional MR imaging. *AJNR Am J Neuroradiol* 2009; **30**: 972–7

- Goode SD, Altaf NA, Auer DP, MacSweeney ST. Improvement in cerebrovascular reserve following carotid endarterectomy using hypercapnia BOLD fMRI. Submitted *Eur J Vasc Endovasc Surg*, deemed potentially acceptable following revision

Presentations

- Recurrent events in patients with carotid artery occlusion as predicted by hypercapnia BOLD fMRI. European Stroke Conference, Nice, May 2008

- *Improvement in cerebrovascular reserve following carotid endarterectomy using hypercapnia BOLD fMRI*. European Society for Vascular Surgery, Nice, September 2008

Prizes

- Presentation prize from Institute of Neuroscience, University of Nottingham

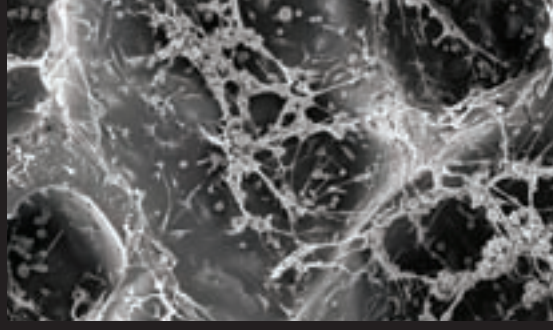
Stroke is the single biggest cause of severe disability and the third most common cause of death (11%) in the UK. What is needed is a means to assess the risk of stroke in the individual patient and to target intervention (carotid endarterectomy (CEA), carotid artery surgery) in those at high risk while avoiding unnecessary intervention in those at lower risk. High risk subgroups can be identified by detecting patients with impaired cerebral haemodynamics. My PhD research work concentrated on examining the role of cerebrovascular reserve (CVR) using new and novel MRI-based techniques.

When I started my work one of the first tasks was to develop and implement a technique of assessing CVR capacity, using hypercapnia blood oxygen level-dependent (BOLD) functional MRI, which combines the advantages of availability and high spatial resolution without the use of radiation. My initial work started in healthy volunteers showing a very good short-term reproducibility and intersubject variability, this work being published in the *American Journal of Neuroradiology*. Following this the work continued in patients with carotid artery disease. In total we scanned 45 patients, of which 18 patients went on to have CEA. The results from this patient work confirm the effect of CO_2 reactivity on the BOLD response in patients with carotid artery disease. We showed that following CEA patients had a significantly improved CVR and that in those patients with an impaired CVR, they are more likely to have recurrent ischaemic symptoms.

I plan to continue the current work further in Sheffield during my academic clinical fellowship in vascular radiology. I hope to continue with further patient scanning using CVR assessment in patients undergoing carotid artery stenting. Another direction of future work is to develop the advanced MRI to assess true oxygen extraction fraction, which can only currently be assessed using high-dose radiation techniques such as PET.

Fig 1 Stephen in MRI scanner having MRI scan
Fig 2 Example of CVR map for patient with RT-sided carotid artery occlusion

Developing new therapies for liver disease: enhancing liver regeneration using targeted intrahepatic growth factor delivery



MR JOHN HAMMOND

Fellowship/sponsor
College Research Fellowship

Supervisor
Mr IJ Beckingham, Professor BJ Rowlands, Dr S Badylak and Professor KM Shakesheff

Site of work
Department of Surgery and Centre for Biomolecular Sciences, University of Nottingham, and McGowan Institute for Regenerative Medicine, University of Pittsburgh

Publications

- Hammond JS, Beckingham IJ, Shakesheff KM. Scaffolds for liver tissue engineering. *Expert Rev Med Devices* 2006; 3: 21–27

Presentations

- American Association for the Study of Liver Diseases, San Francisco, November 2008
- Society of Academic and Research Surgery, Patey Session, Cambridge, January 2007

Prizes

- *Scaffolds for liver regeneration: using growth factors to enhance liver regeneration after partial hepatectomy*. McCallum Prize, Med-Chi Society, Nottingham, June 2008

There have been major advances in liver resection surgery for liver cancer in the past three decades. However, the size of resection remains limited by the need to retain an adequate post-resection residual liver volume. Developing strategies that boost functional liver capacity or enhance its rate of healing may promote faster patient recovery and reduce rates of disease recurrence.

The aim of this project was to develop a growth factor delivery device that could be implanted directly into the liver, where it would promote growth and enhance liver healing. The work was undertaken in two phases: an in vitro phase, in which the delivery device was designed and optimised for intrahepatic use; and an in vivo phase, in which the system was trialled in normal liver tissue and liver that had undergone liver resection.

The project was an original concept that brought together advances in the field of regenerative medicine and drug delivery, and formed the basis for collaboration between the department of surgery in Nottingham and tissue engineering groups in Nottingham and Pittsburgh.

I completed the body of work set out in the project application, successfully developing the growth factor delivery device and demonstrating its ability to modulate liver growth. In the process I had the opportunity to undertake a research fellowship at the McGowan Institute for Regenerative Medicine and the Liver Cancer Centre at University of Pittsburgh Medical Center. I have since submitted my PhD thesis and secured a clinical lecturership in surgery with the Nottingham Digestive Diseases Centre, where I continue work on liver surgery and regeneration. The next phase of the project is to refine the delivery technology and scale up the system towards our goal of use in the clinic.

Fig 1 Electron micrograph of liver cells growing on a scaffold
Fig 2 John on the microscope

The role of central and peripheral factors in visceral hyperalgesia associated with diverticular disease

MR DAVID JAMES HUMES

Fellowship/sponsor
Joint College/Research into Ageing Research Fellowship

Supervisor
Professor JH Scholefield and Professor RC Spiller

Site of work
Wolfson Digestive Diseases Centre, University of Nottingham

Publications

- Humes DJ, Solaymani-Dodaran M, Fleming KM *et al.* A population-based study of perforated diverticular disease incidence and associated mortality. *Gastroenterology* 2009; **136**: 1,198–205
- Humes DJ, Simpson J, Neal KR *et al.* Psychological and colonic factors in painful diverticulosis. *Br J Surg* 2008; **95**: 195–8

Presentations

- Neurogastroenterology and Motility 2008, Lucerne, Switzerland, November 2008
- Digestive Disease Week, San Diego, USA, May 2008

Prizes

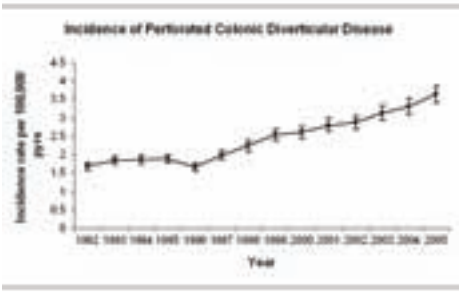
- First prize oral presentation at the University of Nottingham Institute of Clinical Research summer meeting 2008
- €1,000 travel grant to attend United European Gastroenterology Week 2008, Vienna, Austria

Two-thirds of people over the age of 65 will develop diverticulosis (outpouchings from the large bowel) and of these 20% will develop symptoms, yet our knowledge of why these symptoms develop is limited and as a consequence we currently have few treatments to offer this large group of patients.

The aim of this project was to investigate the origin of symptoms in patients with diverticular disease, a condition characterised by small outpouchings from the large bowel associated with recurrent abdominal pain and altered bowel habit, which typically occurs in older people and for which there are currently no effective treatments.

We used a number of techniques to investigate these symptoms, which built on previous work we have undertaken. To date we have carried out a study documenting symptoms in patients with diverticular disease over time and used a large database of general practice patients to identify risk factor for developing complications of having these outpouchings, particularly perforation. We have also investigated how patients with diverticular disease respond to painful rectal stimuli using balloon distension and have investigated the role of inflammation and alterations in the bowel nerves as a possible mechanism.

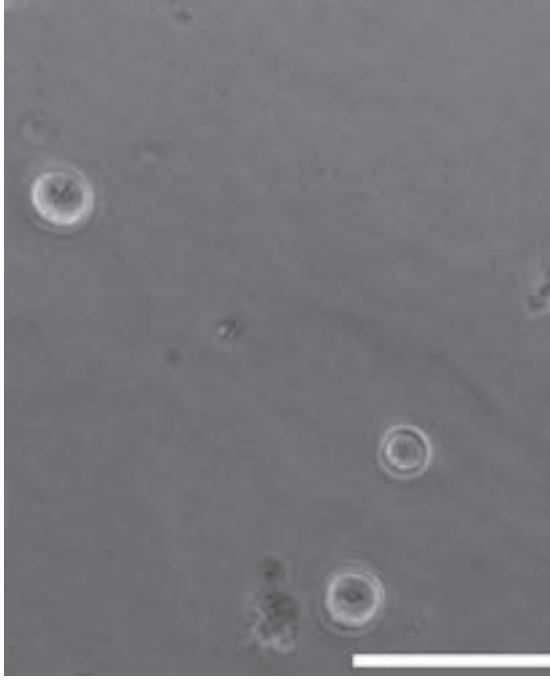
These studies have found that prior inflammation of the bowel leads to a fourfold increase in the reporting of pain in patients with diverticular disease and that increased anxiety leads to a twofold increase in symptom reporting. Using the database we were able to demonstrate a twofold increase in the number of patients developing perforated diverticular disease over 16 years (Figure 3) and estimate the excess mortality associated with perforation. The rectal distension study demonstrated that patients have lower pain thresholds to painful distension and this is associated with an increase in inflammatory markers in the bowel and alterations in the nerve receptors.



We are now using these results to perform a trial of mesalazine (an anti-inflammatory medication) in patients with diverticular disease. We are also investigating the brain's response to painful stimuli using MRI in diverticular disease patients. I am currently working on a study to identify risk factors for developing complications associated with diverticular disease.

Fig 1 Mr D Humes and Dr L Marciani conducting an MRI experiment using painful rectal distension
Fig 2 David with a patient taking part in a randomised controlled trial of mesalazine in patients with symptomatic diverticular disease
Fig 3 Graph of the increase in incidence of perforated diverticular disease over 16 years

Lapatinib selectively inhibits HER-2 positive pre-invasive breast cancer stem cells



Pre-invasive breast cancer represents 25% of screened detected breast lesions.

Cancer stem cells (CSCs) divide and rapidly proliferate to constitute the main bulk of a tumour mass. Current therapeutic strategies such as chemotherapy target these rapidly dividing cells leading to cancer remission but the CSC avoids such treatments, survives and eventually undergoes further cell division leading to tumour recurrence. It is therefore important that we develop treatments to target the CSC.

In breast cancer, 20–30 % of screen-detected cancers are pre-invasive lesions. If untreated they will become invasive in 40–50 % of cases. Pre-invasive lesions express receptors, such as HER-2, which are targets for specific treatments. Lapatinib is one such inhibitor with the potential to treat HER-2 positive DCIS.

For the first time, this research has utilised the mammosphere (MS) culture method to determine the effects of Lapatinib on CSC. The MS (non-adherent) culture system is a method that can be used to isolate CSC. Using several breast cancer cell lines, as well as patient tissue samples, Lapatinib was shown to inhibit MS formation in the HER-2 positive cells through a significant reduction in proliferation. Alongside the MS work a 3D culture system able to simulate the features of the breast ducts has been used. Lapatinib markedly decreased the size of the HER-2 positive colonies formed again through a reduction in proliferation supporting the results shown in the MS model.

In conclusion, Lapatinib has the potential to be used as an adjuvant treatment for HER-2 positive pre-invasive breast cancer with the ability to target CSC, preventing recurrence and the development of invasive breast cancer.

Fig 1 A) Compact colonies representative of primary DCIS in 3D matrigel culture, B) Brightfield images demonstrating the impact of lapatinib on colony size (i) in the absence of Lapatinib, and (ii) in the presence of Lapatinib

Fig 2 Rachael analysing samples in the laboratory

MISS RACHAEL LOUISE JOHNSON

Fellowship/sponsor
College Research Fellowship

Supervisor
Professor Nigel Bundred

Site of work
Paterson Institute for Cancer Research

Presentations

- San Antonio Breast Cancer Symposium, Texas, 2008
- British Association of Surgical Oncology, The Royal College of Surgeons of England, London, 2008

Prizes

- American Association of Cancer Research, International Scholar-in-Training Award, received December 2008, San Antonio Breast Cancer Symposium
- BJS Prize, awarded November 2008, Association of Breast Surgery at BASO and BASO ACS Joint Scientific Conference

Metabolic profiling of intestinal ischaemia/reperfusion

Between 1995 and 2005 the number of patients with severe sepsis admitted to critical care units in the UK increased from 18,500 to 31,000 cases and despite improvements in the delivery of intensive care, mortality rates remain at 20–50%. Severe sepsis therefore represents a growing epidemic with a significant associated economic burden.

MR JAMES KINROSS

Fellowship/sponsor
With support from the Rosetrees Trust and the Eranda Foundation

Supervisor
Professor the Lord Darzi of Denham

Site of work
St Mary's Hospital, Imperial College London

Publications

- Kinross J, Warren O, Basson S *et al*. Intestinal ischemia/reperfusion injury: defining the role of the gut microbiome (2009). *Biomarkers in Medicine* 2009; **3**: 175–92

- Kinross JM, von Roon AC, Holmes E *et al*. The human gut microbiome: implications for future health care. *Current Gastroenterol Rep* 2008; **10**: 396–403

Presentations

- Kinross J, Holmes E, Nicholson J. *Metabonomic profiling of the gut microbiome: Implications for human health*. Metagenomics 2008, University College San Diego, November 2008

- Kinross J, Barton R, Alkhamesi N *et al*. *Surgical Supersystems: Metabonomic profiling of the gut microbiome during surgically induced intestinal ischaemia / reperfusion injury*. 9th International Conference on Systems Biology, Gothenburg 2008

Prizes

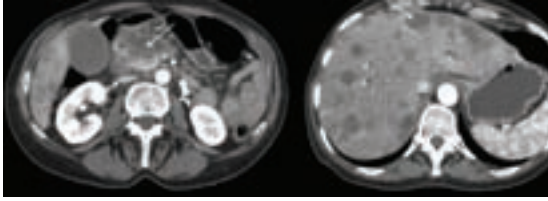
- Best poster award: *Metabonomic profiling of intestinal ischaemia/reperfusion in the rat*. Imperial College London, annual surgical research meeting, December 2007

The aim of this study is to prevent post-operative sepsis by diagnosing and preventing intestinal ischaemia/reperfusion (I/R) injury. Patients undergoing major surgery or those suffering trauma are exposed to a reduced intestinal blood supply, resulting in hypoperfusion. Successful treatment or 'reperfusion' paradoxically exacerbates this injury, triggering a systemic inflammatory response, sepsis and multi-organ failure. Gut bacteria play an important role in this mechanism; however, their role has yet to be fully elucidated.

Nuclear Magnetic Resonance (NMR) spectroscopy was used in combination with multivariate statistical analysis to study the complete metabolic response of animals to intestinal I/R. It also used genomic strategies to analyse the response of the intestinal microbial ecosystem (the microbiome) and to define the metabolic role of the gut microbiota during intestinal I/R. Finally, this project modulated the intestinal microbiome through the administration of preoperative prebiotic foodstuffs (or non-digestible complex sugars) to improve post-operative outcome.

Data suggest that metabolic profiles of both urine and plasma offer an accurate diagnosis of intestinal I/R more effectively than is currently possible with standard laboratory tests. Furthermore, it is able to detect fluctuations in the gut microbial metabolites caused by I/R injury non-invasively. Genomic analysis demonstrates that commensal (ie 'friendly') populations of bacteria are adversely affected by intestinal I/R and that they may be protected by the preoperative use of a galactooligosaccharide prebiotic. Preliminary data also suggest that this may improve morbidity after intestinal I/R injury. This research challenges how we perceive the biology of surgical patients. In essence, we are a complex biological supersystem made up of trillions of essential microbiota that directly influence our response to surgical insults. The work will now be taken on to a clinical study, which aims to reduce rates of postoperative sepsis through nutritional modulation of the gut flora.

Fig 1 James working in the laboratory at St Mary's Hospital London
Fig 2 NMR: a 600MHz 1HNMR spectroscope used by James to carry out metabolic analysis of biofluids



Role of the notch pathway in pancreatic cancer

Pancreatic cancer is the fifth most common cause of cancer-related death in the UK. Only 12% of patients diagnosed with pancreatic cancer survive for 12 months following diagnosis.

Pancreatic cancer is a devastating disease, which often presents at an advanced stage when surgery to remove the cancer is not possible. It is also largely resistant to current chemotherapy drugs and therefore has a dismal prognosis. Normal cells are dependent upon complex networks of signalling chemicals within the cell in order to perform their normal functions. In cancer cells these signalling networks become disordered resulting in cancer growth, invasion and spread. In addition, a number of signalling networks that are usually inactivated in adult cells become reactivated. The aim of this project was to investigate the role of one of these signalling pathways, called Notch, in pancreatic cancer and to determine if this could provide a target for future treatments.

This was a science project and experiments were performed on pancreatic cancer cells and tumour tissue taken from patients having undergone surgery for the disease. The study found that the Notch pathway was reactivated in pancreatic cancer and that higher levels of activation were associated with poorer long-term survival following surgery for the disease. In addition, inactivation of the pathway in pancreatic cancer cells using a drug called a gamma-secretase inhibitor resulted in reduced cancer cell growth and increased death of cancer cells. This was particularly pronounced when used with gemcitabine, the current chemotherapy drug of choice in this disease. Additionally, a technique called mass spectroscopy has been used to identify a fragment of Notch in the blood of patients with pancreatic cancer, which may yield a new diagnostic tool to enable earlier detection of the disease.

The results of this study indicate that the Notch pathway is important in pancreatic cancer and that this information may aid earlier detection of the disease and help predict patient prognosis. Furthermore, targeting this pathway using gamma-secretase inhibitors offers a promising treatment to these patients in the future.

MR CHRIS MANN

Fellowship/sponsor
With support from Sir Samuel Scott of Yews Trust

Supervisor
Mr David Berry and Professor Maggie Manson

Site of work
University of Leicester and University Hospitals of Leicester

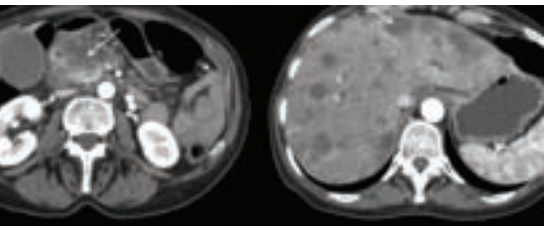
Publications

- Mann CD, Neal CP, Garcea G *et al.* Prognostic molecular markers in hepatocellular carcinoma: A systematic review. *Eur J Cancer 2007;* **43**: 979–92
- Doucas H, Mann CD, Sutton CD *et al.* Expression of nuclear notch3 in pancreatic adenocarcinomas is associated with adverse clinical features, and correlates with the expression of STAT3 and phosphorylated *Akt. J Surg Oncol* 2008; **97**: 63–68

Presentations

- 8th Congress of the European Chapter of the International Hepato-Pancreato-Biliary Association, Athens, June 2009
- National Cancer Research Institute, Birmingham, October 2009

Fig 1 A CT scan from a patient with advanced pancreatic cancer, showing the pancreatic cancer (left arrow) and metastases (spread) in the liver (right arrow)
Fig 2 Chris with supervisor, Professor Maggie Manson, discussing results



avß6 as a prognostic indicator and therapeutic target for antibody-targeted magnetic fluid hyperthermia in squamous cell carcinoma

MR DANIEL JAMES MARSH

Fellowship/sponsor
Blond McIndoe Research Fellowship

Supervisor
Mr Jag Chana and Professor Kerry Chester

Site of work
RAFT/UCL Cancer Institute

Publications

- Marsh D, Dickinson S, Neill GW *et al.* alpha vbeta 6 Integrin promotes the invasion of morphoeic basal cell carcinoma through stromal modulation. *Cancer Res* 2008; **68**: 3,295–303
- Kogelberg H, Tolner B, Thomas GJ *et al.* Engineering a single-chain Fv antibody to alpha v beta 6 integrin using the specificity-determining loop of a foot-and-mouth disease virus. *J Mol Biol* 2008; **382**: 385–401

Presentations

- *Antibody targeted magnetic fluid hyperthermia for therapy in oral cancer.* Royal Society of Medicine, Sylvia Lawler Prize meeting, London, July 2009
- *The avβ6 integrin – a potential target for antibody conjugated magnetic fluid hyperthermia in head and neck squamous cell carcinoma.* Oral presentation, British Association of Surgical Oncology, The Royal College of Surgeons of England, London, November 2008

Prizes

- Ronald Raven Prize, British Association of Surgical Oncology, The Royal College of Surgeons of England, London, November 2008
- Paton Masser Memorial Prize, British Association of Plastic, Reconstructive and Aesthetic Surgeons, December 2007

Head and neck squamous cell carcinoma is an aggressive disease, largely unresponsive to current therapies and one that has seen little improvement in prognosis over the past 25 years.

Head and neck cancer is a relatively understudied disease but one that causes significant morbidity and mortality. 75 % of patients with advanced head and neck cancer will not survive beyond five years from their diagnosis. Current research involves combining current chemo and radiotherapies in an attempt to prolong patient survival. This project has two objectives – first, to identify if there is a more accurate way of determining patient prognosis and second, to develop a novel way of treating patients with advanced disease.

The avβ6 integrin is a molecular target displayed primarily on cancerous cells and not on normal healthy tissues, making it an ideal target for anti-cancer therapies. This project first looked at whether patients with high levels of avβ6 had a poorer prognosis than those with low levels. We found that while there was no direct link between avβ6 and patients with poor prognosis, we did identify another factor, SMA, which was directly linked to prognosis and found to be a stronger indicator of it than standard clinico-pathological indicators currently in use. Magnetic fluid hyperthermia is a technique using iron nanoparticles to deliver heat therapy, which has been shown to be effective in killing cancer cells. Currently this technique has been used by directly injecting the nanoparticles into the cancerous tumour. We have developed a method of targeting these iron nanoparticles directly to the cancer cells, avoiding the side effects of damage to healthy cells currently seen with conventional anti-cancer therapies.

This is a long-term project, which continues with the development of magnetic fluid hyperthermia for therapy in other cancer types, in particular melanoma. The long term aim of this research is to develop an injectable cancer treatment that targets and treats both the primary tumour and any tiny metastatic deposits that currently may lie undetected.

Fig 1 Daniel in theatre with his supervisor, Jagdeep Chana
Fig 2 Typical intra-oral squamous cell carcinoma

Hypoxia-regulated microRNAs in cancer

MR ROBERT IAIN MCCORMICK

Fellowship/sponsor
Legacy of Mr DFG Clark

Supervisor
Professor Adrian L Harris

Site of work
Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, University of Oxford

Publications

- Favoro E, Ramachandaran A, McCormick R *et al.* Hypoxia-induced miR-210 regulates mitochondrial metabolism and Krebs cycle in cancer by repression of iron sulphur complex protein ISCU. Submitted to *Nature Medicine*, June 2009

Presentations

- *Renal tumours in vHL syndrome*. Royal Society of Medicine urology winter meeting, February 2008
- *Hypoxia regulated microRNAs in cancer*. Joint Mount Vernon Cancer Network and Thames Valley Network renal cancer day, June 2009

Fifty per cent of patients diagnosed with kidney cancer will die of this disease.

Kidney cancer is the third most common urological cancer but it is potentially the most deadly, with 50 % of those diagnosed dying of the disease. It is frequently diagnosed at an advanced stage and disease that cannot be cured by surgical means is usually fatal.

A major interest in cancer research is the concept that inhibiting the development of blood vessels in tumours should reduce their ability to grow and spread. This process, called angiogenesis, is controlled by a series of molecular signalling events that centre around a response to the low-oxygen conditions (hypoxia) caused when cells do not have sufficient blood supply. My research has looked at microRNAs, which are molecules that control the production of protein from the genes, and form an important regulatory framework in the cell.

Using low-oxygen incubators we were able to identify microRNAs that became much more abundant in hypoxic conditions and thus may be important in angiogenesis, or increased survival of tumour cells in hypoxia. We demonstrated that one such molecule, miR-210, was up-regulated (became more concentrated) in kidney tumours compared to normal tissue, by a factor of up to 100-fold. This was achieved by examining the genes in both normal and tumour tissues from kidneys removed at operation. Work using cancer cells grown in the laboratory has identified an important role of miR-210 in regulating a protein that is instrumental in controlling oxygen-dependent energy production in the cell.

Our work to date has suggested that miR-210 is important in the biology of kidney cancer, among other types. Research fellowships such as those offered by the Royal College of Surgeons will allow us to continue to work towards further understanding of this disease in collaboration with departments such as the Weatherall Institute of Molecular Medicine, through clinical lecturer programmes and academic clinical fellowships within the urology department.

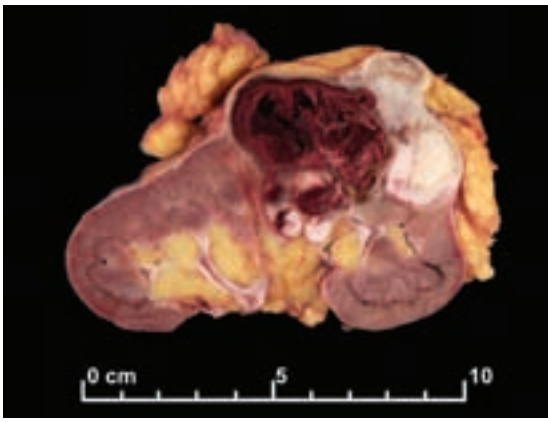
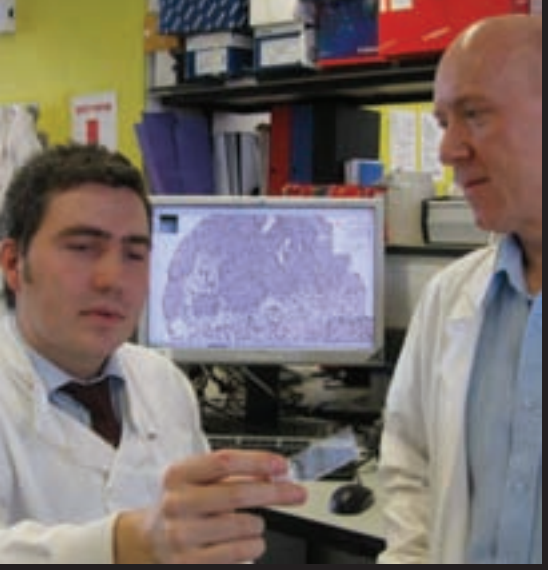


Fig 1 Rob using a low-oxygen incubator, a vital tool in angiogenesis research
Fig 2 A kidney tumour expanding into the surrounding fat



Abnormal MEK5/ERK5 signalling in prostate cancer: potential for clinical application

MR STUART MCCRACKEN

Fellowship/sponsor
Joint College/Dunhill Medical Trust Research Fellowship

Supervisor
Professor HY Leung and Professor CN Robson

Site of work
Northern Institute for Cancer Research, Newcastle University

Publications

- McCracken SR, Ramsay A, Heer R *et al.* Aberrant expression of extracellular signal-regulated kinase 5 in human prostate cancer. *Oncogene* 2008; **27**: 2,978–88
- Dudderidge TJ, McCracken SR, Loddo M *et al.* Mitogenic growth signalling, DNA replication licensing, and survival are linked in prostate cancer. *Br J Cancer* 2007; **96**: 1,384–93

Presentations

- McCracken S, Mathers M, Edwards J *et al. Abnormal ERK5 Expression is Associated with Metastatic, Androgen-Independent Human Prostate Cancer and Stimulates Proliferation, Migration, Invasion and MMP-1, -2 and -9 Expression.* European Association of Urologists Annual Meeting, Paris 2006
- McCracken SRC, Jenkins BL, Heer R et al. *Expression Analysis of the MEK5/ERK5 Signalling Pathway in Human Prostate Cancer.* British Association of Urological Surgeons annual meeting, Glasgow 2005

Prizes

- European Association of Urology prize for the best paper published on fundamental research in European literature, 2008

Prostate cancer is the most common cancer in men in the UK, accounting for nearly a quarter of all new male cancer diagnoses (nearly 35,000 men diagnosed each year in the UK) and the second leading cause of cancer death in men after lung cancer. The mean age of patients with this disorder is 72–74 years and about 85% of patients are diagnosed after age 65 years.

My research has focused on the MEK5/ERK5 signalling pathway, one of the MAP kinase pathways, which are major information highways carrying messages from receptors on the surface of a cell, relaying messages to targets in the nucleus. These pathways are utilised by the cell in normal cellular processes, including proliferation and programmed cell death, and it is therefore perhaps not surprising that deregulation of these pathways have been implicated in carcinogenesis.

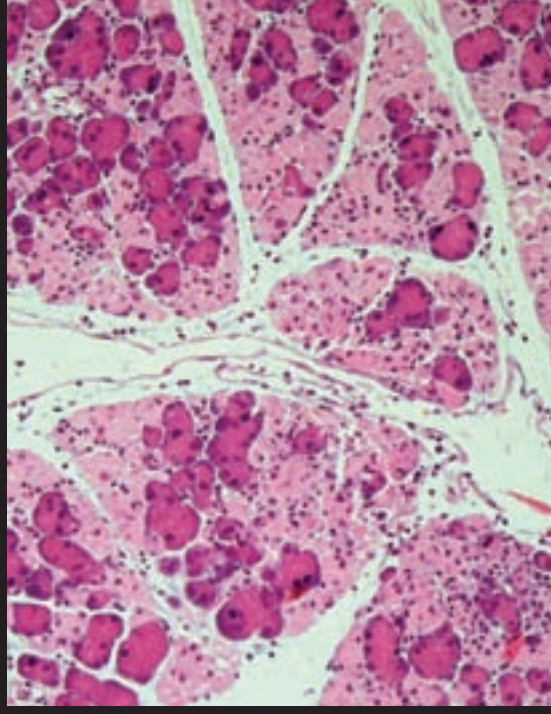
I have shown that ERK5 protein levels are overexpressed in prostate cancer and those cases with the worst prognosis, those with bone metastases or those with locally advanced disease at diagnosis, have the highest ERK5 levels. Those patients with ERK5 staining present in the nucleus have a particularly poor prognosis. In resting prostate cancer cells I have shown that ERK5 resides in the cytoplasm but on stimulation with EGF, ERK5 localises to the nucleus, similar to that observed in aggressive clinical disease.

I then stably overexpressed ERK5 in a prostate cancer cell line and was able to show that compared to an identical control cell line, the overexpressing line behaved more aggressively, showing increased proliferation, migrative and invasive ability. I then injected the two different types of cells subcutaneously and demonstrated in an animal model that overexpressing ERK5 leads to more aggressive disease, with the subcutaneous tumours growing much quicker in the ERK5 overexpressing experimental group.

I then utilised a small molecule inhibitor, which prevents activation of ERK5 and showed reduced proliferation, migration and invasion in prostate cancer cell treated with the inhibitor providing more evidence to highlight the attractiveness of the MEK5/ERK5 pathway as a target in prostate cancer treatment. As a direct consequence of results gained in this period of research, drugs specific to the MEK5/ERK5 pathway are currently being developed for eventual phase I study in patients with advanced prostate cancer.

Fig 1 Stuart and supervisor Professor Craig Robson discuss microarray results

Determinants of severity in acute pancreatitis



Acute pancreatitis is a commonly treated disease that causes severe illness, prolonged disability and even death in about one-fifth of patients.

Acute pancreatitis is a sudden inflammation of the pancreas, most often caused by either gallstones or excessive alcohol intake. While a mild, self-limiting attack occurs in most patients in approximately one-fifth a severe inflammation results, causing serious illness, prolonged disability and even death. Current interventions are limited to supporting the body while the illness runs its course. A full understanding of the workings of the pancreas is now thought to be necessary in order to lead to a new generation of therapy.

This research project explored the role specific genes play in controlling the way pancreas cells die in response to injury. An injured pancreas cell dies either in a controlled fashion (called apoptosis) or in an uncontrolled fashion (called necrosis). If the majority of cells die by apoptosis, this is suggested to favour a milder disease. Animal models of pancreatitis were used with either apoptotic or necrotic genes knocked out (removed). Severity was measured by examining the tissue microscopically for damage and by measuring particular chemicals that are known to rise in pancreatitis. Preliminary results have shown differences between the knock-out groups and will provide information for further research.

In addition, collaborative work on human pancreatic tissue donated by patients undergoing pancreatic surgery has revealed further information on cell function. This published work has confirmed that human cells react to chemical stimulants in very similar ways to common animal models of pancreatitis, thus validating previous laboratory work.

This research project has built on work previously undertaken within the division of surgery and oncology (Royal Liverpool University Hospital) and the department of physiology (University of Liverpool). This very successful and productive collaboration has supported research fellows for over 15 years and the work undertaken in this project will contribute to the future investigations of the group.

Fig 1 Microscope views of typical appearances of necrosis and inflammation in severe pancreatitis
Fig 2 Mr McLaughlin reviewing a patient on the surgical ward round

MR EUAN MCLAUGHLIN

Fellowship/sponsor
Sir Alan Parks Research Fellowship

Supervisor
Professor R Sutton

Site of work
Royal Liverpool University Hospital

Presentations

- American Pancreatic Association, Chicago, USA, November 2007
- Pancreatic Society of Great Britain and Ireland annual meeting, University College London, November 2007

Novel targets for the prevention of endothelial leakage in severe burns

Dysfunction of the immune and inflammatory systems plays a pivotal role in burn-associated mortality.

MR CHRIS MILNER

Fellowship/sponsor
Joint College/Healing Foundation Research Fellowship

Supervisor
Dr Nicholas P Brindle

Site of work
University of Leicester

Publications

- Milner CS, Hansen TM, Singh H, Brindle NP. Roles of the receptor tyrosine kinases Tie1 and Tie2 in mediating the effects of angiopoietin-1 on endothelial permeability and apoptosis. *Microvasc Res* 2009; **77**: 187–91
- Singh H, Milner CS, Aguilar Hernandez MM *et al*. Vascular endothelial growth factor activates the Tie family of receptor tyrosine kinases. *Cell Signal* 2009; **21**: 1,346–50

Presentations

- Australia and New Zealand Burn Association (ANZBA), Perth, Australia, September 2007
- Summer BAPRAS scientific meeting, Deauville, France, July 2007

Prizes

- Merit award for scientific and research presentation at the ANZBA annual meeting 15 September 2007

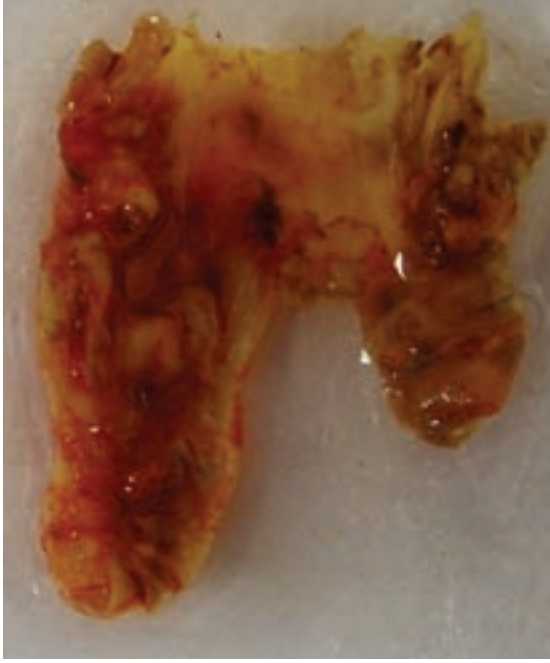
While major burn injury has obvious effects through scarring it also triggers widespread and uncontrolled inflammation throughout the body, leading to internal organ damage that can be severe enough to cause death. This inflammatory response is strongly promoted by the widespread 'activation' of the blood vessel lining (known as the endothelium) and recent international research has identified the endothelium as a valuable target for new anti-inflammatory treatments. One potential drug known to work on the endothelium is angiopoietin-1 and my research project studied this drug in a variety of laboratory conditions that recreated the inflammatory responses involved with major burns.

Results from this research have now identified the specific endothelial receptor mechanism that produces the anti-inflammatory effects associated with angiopoietin-1. The work has also demonstrated provisional anti-inflammatory effects of angiopoietin-1 when using the drug in conjunction with blood samples from seriously ill patients with sepsis. Following this and other international research in the area, angiopoietin-1 offers great therapeutic potential by suppressing unwanted systemic inflammation. Furthermore, existing pre-clinical experiments indicate that angiopoietin-1 has few unwanted side effects and is actually associated with other benefits such as accelerated wound healing.

If the beneficial effects of angiopoietin-1 continue to be evident in future clinical trials using the drug this could potentially offer a great improvement in the medical care of patients with major burns, including reduced duration of ITU care, earlier skin grafting and ultimately a reduction in mortality rates. Following on from this study the leads gained have been handed on to new researchers who continue to build upon the data gathered over the last two years, ultimately aiming towards better care for both patients with major burns and other inflammation-based critical illnesses.

Fig 1 Burns come in all shapes and sizes but all require specialist care to get the best outcome.
Fig 2 Healed burns still pose significant problems for patients, as shown here where a burn contracture is being released to improve arm function.

A double-blind placebo-controlled study to evaluate the effect of raising plasma high-density lipoprotein concentration on carotid plaque stability



MR HOSAAM NASR

Fellowship/sponsor
Joint College/Dunhill Medical Trust Research Fellowship

Supervisor
Mr Ian Loftus, Professor Matt Thompson and Dr Gillian Cockerill

Site of work
St George's University of London

Publications
- Results have to be approved by Pfizer and CSL prior to publishing any work

Presentations
- American Heart Association, Orlando, November 2007
- Vascular Surgical Society, Manchester, December 2007

Stroke is the third most common cause of death in England and Wales after heart disease and cancer. In the UK strokes account for 9% of all deaths in men and 13% in women. Despite the improved treatments with current interventions a lot of research is still needed to reduce further its impact on individuals and society.

Atherosclerosis is a chronic progressive disease that affects large and medium-sized blood vessels. In the advanced stages of the disease this will lead to the development of the atherosclerotic plaque. Plaque instability and rupture is responsible for the high risk of a disabling stroke following a transient ischaemic attack (mini-stroke). The currently accepted best medical intervention to reduce this risk of stroke is by surgical removal of the plaque (carotid endarterectomy). Unfortunately, due to plaque instability this procedure still carries a relatively high risk of stroke and death of up to 7 %. Therefore, plaque stabilisation is an attractive therapeutic target.

High-density lipoprotein (HDL) is a naturally circulating product that possesses many antiatherogenic and plaque-stabilising properties. Its acute anti-inflammatory, antioxidant and antithrombotic effects lead us to believe that it can acutely alter the unstable plaque phenotype (characteristics) into a more stable one.

To test this hypothesis we recruited 40 patients undergoing carotid endarterectomy (CEA) following a recent stroke or mini-stroke. Patients were then randomised to an infusion of reconstituted HDL (rHDL) at a concentration of 40mg/kg, or an equivalent volume of saline. We then tested the effects of rHDL on genes (tissue factor and thrombomodulin) and proteins (MMP-9, Interlukin-6 and Monocyte chemotactic protein-1) known to be associated with plaque instability.

Although we were not able to demonstrate any effect of rHDL on genes associated with plaque instability, we have shown that it acutely reduces circulating levels of all the abovementioned proteins. Theoretically these results indicate that rHDL infusion may reduce the mortality and morbidity associated with CEA. Given the current findings it would appear prudent to suggest further studies to evaluate the clinical effects of rHDL infusion on neurological recovery and operative mortality and morbidity.

Fig 1 An unstable carotid plaque with evidence of bleeding into the vessel wall
Fig 2 Hosaam preparing carotid plaques for mRNA extraction (or gene extraction)

Bioluminescence-mediated photodynamic therapy for gliomas

Gliomas, the commonest of brain tumours, are the sixth leading cause of cancer death in adults.

MISS JANE NG

Fellowship/sponsor
With support from the Rosetrees Trust and the legacy of Mr John Stafford

Supervisor
Mr N Kitchen, Professor S Bown and Dr N Henriquez

Site of work
Institute of Neurology

Publications

- Society of British Neurological Surgeons, Birmingham, April 2009
- World Federation of Neurosurgical Societies, Boston, August 2009

Prizes

- British Journal of Neurosurgery prize, 2009

The commonest brain cancer, glioma, is the sixth leading cause of cancer death, with an average survival of no more than one year. Surgery, radiotherapy and chemotherapy have modest benefit. Diffuse infiltration beyond the primary tumour mass is a key feature that makes treatment so difficult. Surgery and radiotherapy fail to address this and chemotherapy is limited by drug penetration, toxicity and drug resistance.

Photodynamic therapy (PDT) is a new treatment that uses special photosensitising drugs that when activated by light of a specific wavelength, interact with oxygen to kill living cells. Within the brain, the uptake of photosensitisers is mainly in cancer tissue, so PDT leaves normal brain largely unharmed. Glioma patients receiving PDT have a comparable survival to those receiving chemotherapy, with considerably fewer side effects. However, because of the infiltrative nature of glioma, light penetration limits the efficacy of PDT. Bioluminescence is the emission of light by a living organism, such as fireflies, and results from the conversion of chemical energy to light energy. The aim of this project is to use the light generated by bioluminescence to activate a photosensitiser and in this way to kill cancer cells. The hope is that this technique can be harnessed and used to target the elusive and invasive glioma cells.

In the laboratory I have genetically engineered glioma cells to produce light by bioluminescence and have used this light to activate a photosensitiser, leading to cell kill. To develop this concept further I plan to transplant these bioluminescent cancer cells into an animal model and see whether bioluminescence-mediated PDT can be demonstrated in a living animal.

The translational potential of this research is significant. Bioluminescence-mediated PDT could provide patients with a novel and non-toxic approach to targeting the diffuse and invasive nature of their disease. In this way, working synergistically with existing therapies that concentrate on loco-regional control, prognosis may begin to be significantly improved.

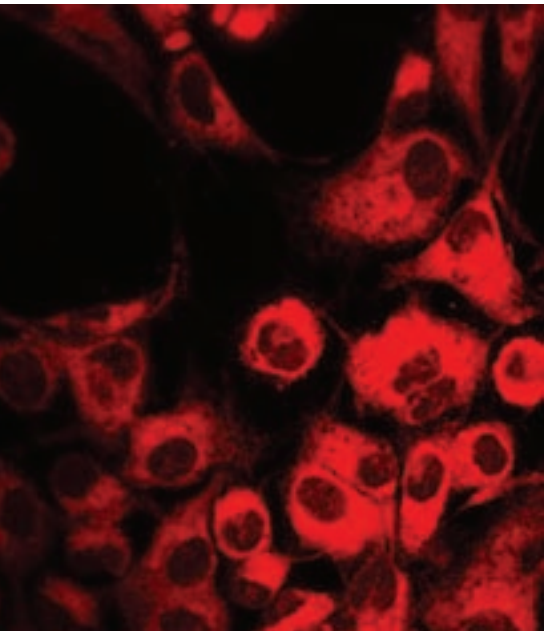


Fig 1 Mr Kitchen planning an operation in a patient who has had a recurrence of glioma
Fig 2 A fluorescent image showing glioma cells that have taken up the photosensitising drug

The role of carbonic anhydrase 9 in tumour biology

CA9 is associated with a poor prognosis in many types of cancer but its function in cancer is poorly understood.

Low levels of oxygen (hypoxia) are found in many different types of cancer. Hypoxia is associated with poor prognosis and resistance to chemotherapy and radiotherapy. Cancer cells adapt to hypoxia by switching on key genes that help them survive. Carbonic anhydrase 9 (CA9) is one of these genes. CA9 is associated with a poor prognosis in many types of cancer but its function is poorly understood. It is thought to play a role in regulating acid levels as cancer tissue is known to be more acidic than healthy tissue. Acidity can cause resistance to certain chemotherapy drugs. I aimed to identify how CA9 helps cancer cells survive.

In order to investigate its function I introduced the CA9 gene into a cancer cell line which has no CA9, creating a new cell line. I compared this new cell line to the original one with no CA9. We studied the effects of CA9 in spheroids (spherical clusters of cells) and showed that the CA9 spheroids had more acid outside cells and less acid inside cells compared to the spheroids with no CA9. CA9 appears to remove acid from inside cancer cells to protect them from the harmful effects of acidity. We also grew tumours in animal models from the cell lines and found that there was more cell death in the CA9 tumours. This may be because the CA9 levels were too high in our artificial model and produced too much acidity outside cells leading to cell death.

Another laboratory will now use the same animal model and measure the acid levels in the growing tumours to see if the CA9 tumours are more acidic. CA9 is a potential target for therapy as blocking its action could reduce tumour survival and improve uptake of certain chemotherapy drugs.

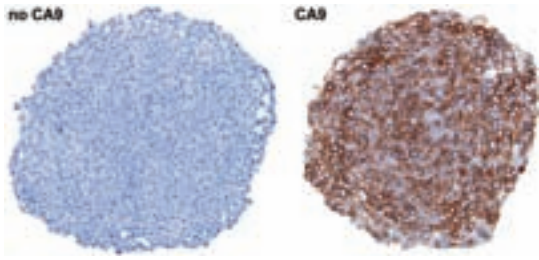


Fig 1 Shalini culturing cancer cells
Fig 2 Spheroids (spherical clusters of cells) with and without CA9

MISS SHALINI PATIAR

Fellowship/sponsor
Dr MP Starritt
Research Fellowship

Supervisor
Professor Adrian Harris

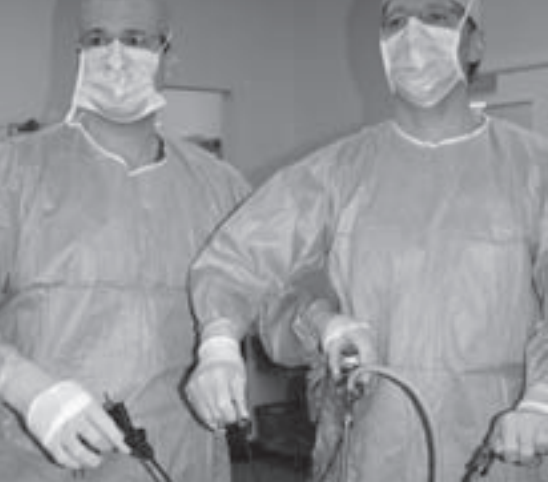
Site of work
Weatherall Institute of Molecular Medicine, University of Oxford

Publications

- Patiar S, Harris AL. Role of hypoxia-inducible factor-1alpha as a cancer therapy target. *Endocr Relat Cancer* 2006; **13(Suppl 1)**: S61–75

Presentations

- National Cancer Research Institute Cancer Conference, Birmingham, UK, 2007
- British Academic Conference in Otolaryngology, Birmingham, UK, 2006



Bowel bacterial flora and bile salts in Roux-en-Y gastric bypass for obesity

MR DIMITRIOS POURNARAS

Fellowship/sponsor
Sir Alan Parks Research Fellowship

Supervisor
Professor Richard Welbourn

Site of work
Musgrove Park Hospital, Taunton

Publications

- Pournaras DJ, le Roux CW. After bariatric surgery what vitamins should be measured and what supplements should be given? *Clin Endocrinol (Oxf)* 2009 Feb 25 [Epub ahead of print]

- Pournaras D, Alagaratnam S, Welbourn R. A career in bariatric surgery: the new metabolic surgery. *BMJ Careers* 2008 May 3: 156–57

Presentations

- Pournaras D *et al.* GLP-1, *Insulin and Insulin Resistance in the First Week After Bariatric Surgery*. 13th World Congress of the International Federation for the Surgery of Obesity Meeting, Buenos Aires, 24–27 September 2008

- Pournaras D *et al. Remission rate of type 2 diabetes is better than for gastric banding.* Association of Laparoscopic Surgeons of Great Britain and Ireland annual meeting, Newcastle, 22–23 September 2007

Prizes

- John Farndon research prize of the Surgical Club of Southwest England for the presentation, *Metabolic Surgery for type 2 diabetes,* November 2008

- Lord Moynihan Second prize for the presentation, *Mechanisms leading to the remission of type 2 diabetes after metabolic surgery*, ASBGI conference, May 2009

Obesity is currently a major cause of premature death in the UK, killing almost 1,000 people a week.

Obesity and diabetes lead to people becoming ill, with reduced quality of life and reduced life expectancy. The most effective treatment for both conditions is bariatric surgery. We aimed to investigate the improved glycaemic control and rate of remission of type 2 diabetes after gastric bypass and gastric banding in a homogeneous population. Moreover, we aimed to explore potential mechanisms.

We conducted a prospective study on patients with type 2 diabetes after gastric bypass or gastric banding over a three-year period. In another group of type 2 diabetic patients undergoing gastric bypass, gastric banding or very low calorie diet, we investigated over a 42-day period: insulin resistance (HOMA-IR), insulin production and glucagon-like peptide 1 (GLP-1) responses after a standard meal. GLP-1 is an incretin, a hormone produced by the gut that enhances insulin secretion. In addition GLP-1 is a satiety gut hormone.

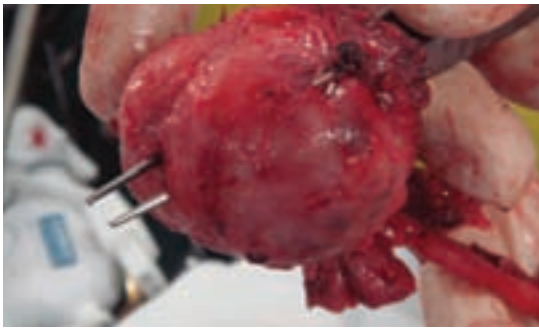
Despite identical weight loss 72% of bypass and 17% of banding patients had a normal fasting glucose off all medication. Within days, patients after bypass but not banding or very low calorie diet had improved insulin resistance, insulin production and GLP-1 responses.

Gastric bypass surgery leads to improved glycaemic control irrespective of weight loss. This is achieved via a reduction in insulin resistance prior to any weight loss and an increase in insulin production. The increased insulin production may be explained by the enhanced GLP-1 production. However, the mechanism via which gastric bypass leads to reduced insulin resistance remains to be elucidated.

Although laparoscopic gastric bypass is now considered a routine operation it is associated with a substantial risk of complications. Once the mechanism of action is identified the current gastric bypass could be modified in order to produce the same effects on diabetes and obesity with a reduced risk of complications.

Fig 1 Dimitrios Pournaras with supervisor Richard Welbourn in the operating theatre performing laparoscopic gastric bypass.

The role of the Sam68 and interacting protein partners in prostate cancer



Prostate cancer is the most common cancer in men the UK with approximately 30,000 new cases diagnosed each year and around 10,000 deaths per annum from the disease in the UK.

The prostate is a small walnut-sized gland located below the bladder in men and produces components of semen. In older men, abnormal cells can form within the gland leading to prostate cancer (PCa), which is a significant cause of death in elderly men. PCa is responsive to testosterone, the major androgen male sex steroid hormone, which causes PCa cells to grow, multiply and spread to other parts of body. Using drugs to block testosterone function in patients can sometimes (but not always) stall progression of PCa and improve the survival of patients.

However, there is no single 'one-size-fits-all' treatment as some cancers grow very quickly (even in the absence of testosterone), while others are slow growing, don't cause the patient any problems during his lifetime and don't need treatment. Subtle changes in proteins in PCa cells appear to make them more likely to grow, multiply and spread rapidly. These proteins differ only very slightly from normal and are generated by a genetic process called 'alternative splicing,' which research suggests is a common phenomenon in cancer.

During my PhD I studied important proteins that regulate 'alternative splicing'. I discovered that a particular protein – Sam68 – was present at unusually high levels in prostates from patients with PCa and that elevated levels of Sam68 enhanced the function of androgens in cells. I also found that androgens could themselves regulate alternative splicing and may affect the behaviour of PCa cells and make them more likely to spread.

Ongoing research in our group involves identification of proteins produced by alternative splicing that cause the worst types of PCa. In the future we hope to identify new ways to detect PCa in patients, decide which individuals require early treatment and find new drugs to kill cancer cells and improve the lives of men with PCa.

Fig 1 Prabhakar Rajan (right) discussing research findings with David Elliott, his supervisor (left), and Caroline Dalgliesh, research associate (centre)
Fig 2 A cancerous prostate gland completely removed from a patient by laparoscopic radical prostatectomy (keyhole surgery)

MR PRABHAKAR RAJAN

Fellowship/sponsor
College Research Fellowship

Supervisor
Dr David J Elliott, Professor Craig N Robson and Professor Hing Y Leung

Site of work
Institute of Human Genetics and Northern Institute for Cancer Research, Newcastle University Trust

Publications

- Rajan P, Gaughan L, Dalgliesh C *et al.* The RNA-binding and adaptor protein Sam68 modulates signal-dependent splicing and transcriptional activity of the androgen receptor. *J Pathol* 2008; **215**: 67–77
- Rajan P, Gaughan L, Dalgliesh C. Regulation of gene expression by the RNA-binding protein Sam68 in cancer. *Biochem Soc Trans 2008;* **36**: 505–7

Presentations

- First International European Alternative Splicing Network Conference on Alternative Splicing, Kraków, Poland, 21–23 May 2008 (oral presentation)
- British Association of Urological Surgeons, section of academic urology annual meeting, The Royal College of Surgeons of England, London, 11 January 2008 (poster demonstration)

Identifying early cartilage changed in knee osteoarthritis

More than one in three individuals over the age of 45 has knee osteoarthritis. There is a 673% projected increase of the number of knee replacements by the year 2030.

Osteoarthritis is a major cause of disability and more than a third of individuals over the age of 45 have knee osteoarthritis. End-stage disease is treated by knee replacement but little is known about earlier changes in the joint and there are currently no disease-modifying treatments. Using the specific pattern of disease shown in Figure 1 our research group has been studying cartilage at different stages of disease.

Our group's previous work showed the abnormal finding of increased type I collagen content in the 'normal' looking cartilage in diseased specimens. My work corroborated this with the finding of the same changes in gene expression. In addition, it was found that cell death plays a role in osteoarthritis and findings show that reactive oxygen species (which include molecules such as free radicals) are implicated. The presence of two proteins has been shown, Bim and FOXO, upstream markers of reactive oxygen species damage.

Above-knee amputations without osteoarthritis have been collected as control specimens and their analysis is nearing completion. They will provide valuable data of aged but not diseased cartilage. Having identified these changes in gene expression and markers of cell death, future work will involve preventing these changes ex vivo, using explanted tissue. The ultimate aim of this work and one of the major challenges facing orthopaedics is being able to prevent, halt or slow osteoarthritis.

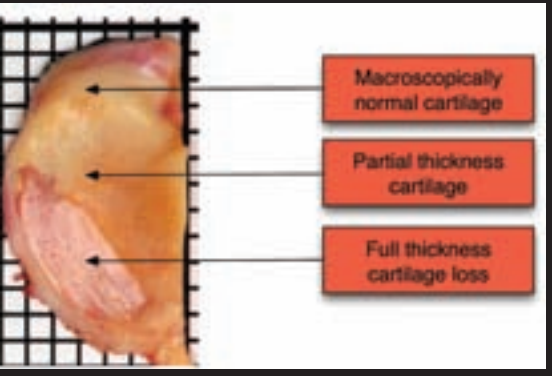


Fig 1 Raj analyses gene expression data
Fig 2 The regions of damage in the type of knee osteoarthritis that is being studied

MR RAJESH ROUT

Fellowship/sponsor
Philip and Lydia Cutner Bequest and Mr JG Taylor Legacy

Supervisor
Mr Andrew Price and Philippa Hulley

Site of work
University of Oxford

Presentations

- 55th annual meeting of the Orthopaedic Research Society, Las Vegas, USA, 2009
- British Orthopaedic Research Society, Manchester, UK, 2008

Prizes

- Girdlestone research prize 2008, Oxford University

Predicting response to chemotherapy in oesophageal cancer

MR ARIN KUMAR SAHA

Fellowship/sponsor
With support from the Rosetrees Trust and Mr Grossman legacy

Supervisor
Mr Henry Sue-Ling, Mr Abeezar Sarela and Dr Laura Hardie

Site of work
Leeds General Infirmary and Leeds Institute for Genetics, Health and Therapeutics

Up to 40% of patients with oesophageal cancer do not respond to chemotherapy. DNA damage assays may be used to predict response and allow tailored cancer care.

Oesophageal cancer has the fastest-growing incidence of all cancers in the Western world and accounts for almost 8,000 deaths per year in the UK alone. Over the past decade it has become increasingly apparent that surgery alone is not sufficient to provide long-term survival and in the UK the standard of treatment for locally advanced oesophageal cancer is chemotherapy followed by surgery. However, balanced against the potential benefits of this approach is the fact that as many as 40 % of patients do not respond to chemotherapy and there are no current methods to predict whether or not a patient will respond.

We looked at DNA damage caused by chemotherapy drugs on oesophageal cancer cells and examined the possibility of using DNA damage assays to predict response to chemotherapy. We took cancer cells from patients before their chemotherapy treatment and exposed these cells to chemotherapy drugs in the laboratory and measured levels of DNA damage. We then correlated these results with the clinical outcome of the patients and whether or not they had responded to treatment. We also looked at the markers associated with response to chemotherapy, results after surgery and long-term survival after chemotherapy and surgery for oesophageal cancer.

We found that patients who responded to chemotherapy had significantly higher levels of DNA damage after our experiments, which suggests that DNA damage assays may have a role to play in predicting response. These results may be the first steps to developing individualised cancer treatment plans and experiments such as these may provide more information to the multi-disciplinary teams that make decisions on the management of this terrible disease. Ultimately, experiments such as these may continue to improve both oncological and surgical outcomes after treatment of oesophageal cancer.

Publications

- Neo-adjuvant chemotherapy and surgery for esophageal adenocarcinoma: prognostic value of circumferential resection margin (CRM) and stratification of N1 category. Accepted for publication *in Ann Surg Oncol*, February 2009
- Saha AK, Sutton CD, Sue-Ling H *et al*. Comparison of oncological outcomes after laparoscopic transhiatal and open esophagectomy for T1 esophageal adenocarcinoma. *Surg Endosc* 2009; **23**: 119–24

Presentations

- Society of Surgical Oncology, Chicago, USA, 2008
- Association of Surgeons of Great Britain and Ireland, Bournemouth, 2008

Prizes

- Leeds Regional Surgical Club gold medal, 2007
- Gut Club best presentation, Leeds, 2008

Fig 1 Characteristic comet assay images illustrating DNA damage after in-vitro exposure of oesophageal cancer cells to chemotherapy drugs

Fig 2 Arin carrying out experiments at the molecular epidemiology unit in the Leeds Institute of Genetics, Health and Therapeutics

Cross-talk between pancreatic cancer cells and stromal monocytes

Pancreatic cancer cells interact with their surrounding cells to enhance their invasive potential.

MR ADNAN AHMED SHEIKH

Fellowship/sponsor
Grand Lodge 250th Anniversary Fund

Supervisor
Dr Eithne Costello

Site of work
Division of surgery and oncology, School of Cancer Studies, University of Liverpool

Publications

- Sheikh AA, Vimalachandran D, Thompson CT *et al.* The expression of S100A8 in pancreatic cancer-associated monocytes is associated with the Smad4 status of pancreatic cancer cells. *Proteomics* 2007; **7**: 1,929–40
- Sheikh A, Ang C, Tonack S *et al.* S100a8 and S100a9 Increase Pancreatic and Colorectal Cancer Cell Motility and Proliferation. *Pancreas* 2008; **37**: 496

Presentations

- American Pancreatic Association 39th annual meeting, Chicago USA 5-8 Nov 2008
- European Pancreatic Club and International Association of Pancreatology, Joint meeting, Łódź Poland, 25-28 June 2008

Prizes

- Travel Bursary from Pancreatic Society of Great Britain and Ireland, July 2008
- Scholarship for research in Pancreatic Cancer from European Pancreatic Club and International Association of Pancreatology, May 2008 and July 2007

Pancreatic cancer is among the most challenging of solid organ malignancies due to its propensity for late presentation, marked with spread to organs around the body. The disease has a dismal outcome, with less than 5 % of patients surviving five years. 'Cross-talk' or communication between cancer cells and the surrounding normal cells has been shown to play an important role in the process of cancer invasiveness and spread.

Using state-of-the-art technology to study proteins, the pancreatic research group at Liverpool studied the protein profile of cancer and their surrounding cells. Two proteins were found to be present in large quantities in the surrounding cells of pancreatic cancer. We therefore aimed to study the interactions of pancreatic cancer cells and their surrounding cells, which express the abovementioned proteins. Arrays of laboratory technologies, such as western blotting, DNA subcloning and protein expression in *E coli* were employed for this.

We demonstrated that factors produced by pancreatic cancer cells cause an induction of S100A8 and S100A9 in the surrounding cells. To further elucidate these interactions we generated S100A8 and S100A9 proteins in the lab using DNA-cloning technology in bacteria. This involves introduction of the DNA sequence for these proteins into a bacterium's DNA, hence allowing for production of these proteins. Once produced the protein can be purified and used in experiments. Experiments using these proteins revealed that growing pancreatic cancer cells in the presence of these proteins significantly increased their growth rate and ability to move, therefore making the cancer more aggressive.

The study of S100A8 and S100A9 in the perspective of pancreatic cancer is unique and has not been undertaken before. These proteins certainly have a role in contributing towards the invasive potential of this disease. Our work has opened avenues for future development and the group is actively pursuing this, having attained further funding. We now aim to understand the cellular mechanisms of how these proteins induce growth and movement of pancreatic cancer. Moreover the potential role of these proteins as treatment targets will also be exploited.

Fig 1 Adnan with Prof Neoptolemos and Dr Costello in the proteomics lab
Fig 2 Adnan setting up an experiment in the tissue culture laboratory

The role of local innate immunity in urinary tract infection

50% of women will experience urinary tract infection in their lifetime and up to 20% of these patients will suffer from recurrent infections.

Cystitis is a common condition of the bladder that is characterised by frequency, urgency and pain during urination. Urinary tract infection (UTI) caused by bacteria is the most common cause and in some patients infection may be recurrent despite no obvious structural abnormality or immune dysfunction. Other patients suffer chronic cystitis in the absence of infection, suggesting a chronic inflammatory condition that could indicate a failure of urinary barrier function. These conditions have significant impact on quality of life but are difficult to treat in the absence of a better understanding.

The urothelium is the tissue that lines the bladder and associated urinary tract, where it forms the main barrier to urine. The aims of this project were to investigate whether the urothelium has receptors that are able to respond to infection and to determine how urinary barrier function is affected by inflammatory mediators. Experiments were performed on normal human urothelial cells taken with consent from patients undergoing urological procedures. The urothelial cells were subjected to a novel method of cell culture to grow a functional urothelial barrier that is representative of how the urothelium behaves in the body.

The results demonstrated that the urothelium possesses bacterial receptors called toll-like receptors (TLR). Urothelial cells were shown to produce immune signals when activated by a protein present on bacteria that cause UTI. This response was inhibited after genetic manipulation to reduce the amount of TLR5 in the cells, suggesting that TLR5 is important in sensing infection by signalling to the immune system.

Unexpectedly, the work showed that urothelium is able to respond to certain immune signals characteristic of inflammation by tightening its barrier, suggesting an adaptive defence mechanism. This opens a new line of research to determine if the protective barrier response is deficient in patients suffering from chronic inflammatory bladder diseases.

MR NICHOLAS SMITH

Fellowship/sponsor
Grand Lodge 250th Anniversary Fund

Supervisor
Professor Jenny Southgate, Dr Ludwik Trejdosiewicz and Mr Ian Eardley

Site of work
University of York

Presentations

- *The innate immune response of human urothelium.* American Urology Association Annual Meeting, Orlando, USA, May 2008
- *The effect of interferon-γ on urothelial barrier function.* British Association of Urological Surgeons annual meeting, Glasgow, June 2007

Prizes

- Prize of the congress president for the best presentation on clinical urology, European Association of Urology Annual congress, Berlin, March 2007

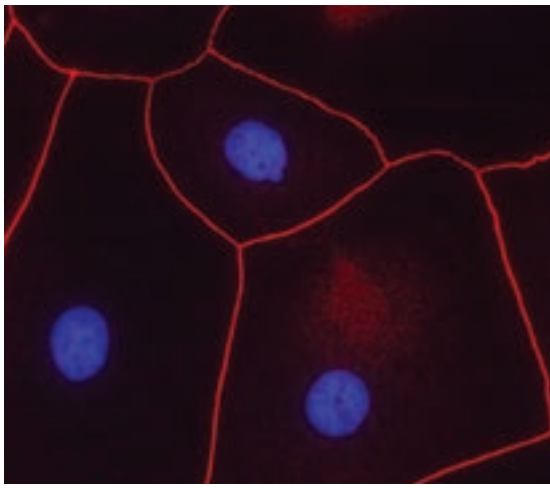


Fig 1 Nick receiving a prize for the research from I Forslund-Larsson (left) and U Jonas (centre) at the European Association of Urology annual congress, Berlin

Fig 2 Looking down on a cultured cell sheet of normal human urothelial cells at high magnification. Cell nuclei are stained blue. An antibody has labelled a protein (zona occludens 1) red that is important in forming a seal between neighbouring cells, causing the cells to form a tight barrier similar to urothelium within the body

Protein expression in colorectal cancer

MISS ELIZABETH TWEEDLE

Fellowship/sponsor
Mr GGT Fletcher Legacy

Supervisor
Mr Paul Rooney and
Dr Eithne Costello

Site of work
Division of surgery and oncology, University of Liverpool

Publications

- Tweedle EM, Ang C, Khattack I *et al.* Low Molecular Weight Heat Shock Protein, HSP27 is a prognostic indicator in rectal cancer. Submitted to *J Clin Oncol*

Presentations

- Tweedle EM, Khattak I, Nedjadi T *et al. Heat shock protein-27 predicts poor survival in rectal, but not colon cancer.* National Cancer Research Institute annual conference, Birmingham, 2008

- Tweedle EM, Sheikh AA, Ang CW *et al. Loss of Smad4 expression is associated with fewer S100A8-positive monocytes in the stroma and poor prognosis in node-negative colorectal cancer.* Colorectal tripartite meeting, Boston, USA, July 2008

Survival from rectal cancer in the UK is around 40% at five years.

Colorectal cancer is diagnosed in one million people worldwide each year. It is a potentially curable disease in the early stages; however, survival is less than 30 % at five years in patients in whom the tumour has spread to lymph nodes or other organs. There are no biomarkers in routine use in colorectal cancer that can predict prognosis. We analysed the proteins expressed in frozen colorectal cancer specimens to determine which proteins may be associated with survival.

Frozen tumours were dissected using laser capture technology to extract the tumour cells from surrounding tissue. Protein from these cells was separated out on to gels. Each gel was compared by computer program to detect variations in protein spots, which were then identified using a tandem mass spectrometer. Immunohistochemistry was used to quantify the protein in 404 paraffin-embedded colorectal cancer specimens and these data were compared to histopathology and survival data.

One protein identified using this method was heat shock protein 27, HSP27. This protein is produced by normal cells when under stress and protects the cell from programmed cell death. We found that it is overproduced in 55 % of colon and rectal cancers. High levels of HSP27 are linked to poor survival in rectal cancer patients, a finding which has not previously been reported. HSP27 may be involved in resistance of some rectal tumours to radio or chemotherapy. This is an area of continued research in collaboration with the Clatterbridge Centre for Oncology, Wirral.

Rectal cancer patients often face months of debilitating chemoradiotherapy and surgical treatment. Reliable biomarkers that predict survival and response to adjuvant treatment are needed in order to tailor therapy to the patient. They may also provide the basis for future treatments. The identification of HSP27 as a prognostic marker in rectal cancer may be the first step towards achieving this goal.

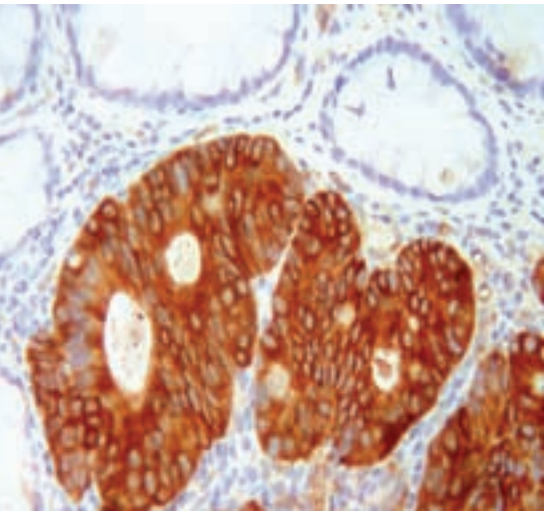
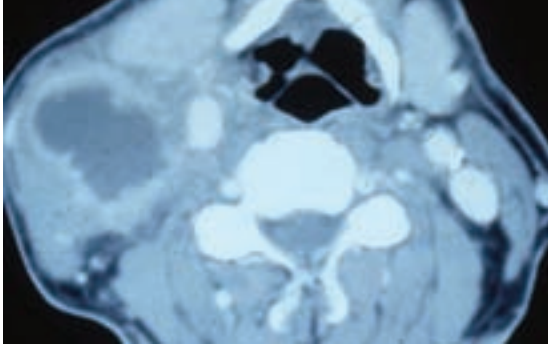


Fig 1 Trainees learning the principles of colorectal surgery
Fig 2 HSP27 staining in colorectal cancer Rectal cancer stained (brown) for HSP27

Oncolytic viral gene therapy for head and neck cancer



The survival of patients with head and neck cancer has not improved over the past three decades.

Head and neck cancer is the sixth most common cancer worldwide. Despite advances in surgery, chemotherapy and radiotherapy, the survival of patients with head and neck cancer has not improved over the past three decades. Therefore, new approaches are needed. Oncolytic viruses are viruses that can infect, replicate in and kill cancer cells. Vaccinia virus was used as the vaccine to eradicate smallpox worldwide. However, it is also an oncolytic virus, which can be genetically modified to deliver gene therapy. All cancers need new blood vessels to supply the nutrients required to enable them to grow and spread. Genes that stop the growth of new blood vessels are called angiogenesis inhibitors. The aim of this project was to develop a new treatment approach to head and neck cancer by using oncolytic vaccinia virus to deliver angiogenesis inhibitors.

Although vaccinia virus has been investigated for cancer therapy, my work was the first to demonstrate the potential for treating head and neck cancer. Using specialist imaging techniques I found that oncolytic vaccinia virus was able to infect, replicate in and kill head and neck cancer cells. Thousands of new viruses were then released from each dead cell selectively, which were able to spread to infect and kill surrounding cancer cells, while sparing normal cells. This limited any side effects. Vaccinia virus was then genetically modified by the insertion of angiogenesis inhibitor genes. The new virus produced high levels of angiogenesis inhibitors, which stopped new blood vessel formation in tumours and slowed their growth, allowing vaccinia virus time to spread through tumours and treat them more effectively. This work will continue and we hope to be able to use vaccinia virus alongside conventional treatments to improve the survival of patients in the future.

MR JAMES RUSSELL TYSOME

Fellowship/sponsor
With support from Euclid Lodge of Installed Masters

Supervisor
Dr Yaohe Wang and Mr Ghassan Alusi

Site of work
Molecular oncology and imaging, Institute of Cancer, Barts and the London Medical School

Publications
- Tysome JR *et al. Gene Therapy* 2009 (in press)
- Tysome JR *et al. Current Opinion in Molecular Therapeutics* 2009 (in press)

Presentations
- American Academy of Otolaryngology – Head and Neck Surgery annual meeting, Chicago, USA, Sep 2008
- American Society of Gene Therapy 11th annual meeting, Boston, USA, May 2008

Prizes
- Xomed-Treace prize, Otorhinolaryngological Research Society, Nottingham, April 2009
- Philip Stell prize, Otorhinolaryngological Research Society, Coventry, April 2008

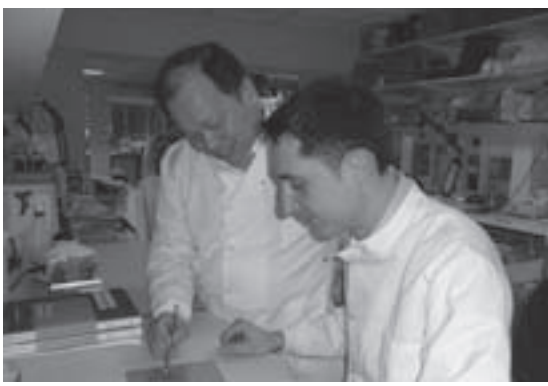


Fig 1 CT scan of a patient with cancer in a lymph gland in their neck
Fig 2 James and Dr Wang discuss the effects of vaccinia virus on head and neck tumours

Biochemical and cellular analysis of a human LOX-1 scavenger receptor

MR RAVINDER SINGH VOHRA

Fellowship/sponsor
Enid Linder Foundation

Supervisor
Professor Shervanthi Homer-Vanniasinkam and Dr Sreenivasan Ponnambalam

Site of work
Endothelial Cell Biology Unit, Leeds Institute of Genetics, Health and Therapeutics Laboratories, University of Leeds

Publications

- Murphy JE, Vohra RS, Dunn S *et al.* Oxidized LDL internalisation by the LOX-1 scavenger receptor is dependent on a novel cytoplasmic motif and regulated by dynamin-2. *J Cell Sci* 2008; **121**: 2,136–47
- Dunn S, Vohra RS, Murphy JE et al. The lectin-like oxidized low-density-lipoprotein receptor: a pro-inflammatory factor in vascular disease. *Biochem J* **409**: 349–55

Presentations

- Vascular Society 2008 annual general meeting, Bournemouth
- Society of Academic and Research Surgery annual conference 2008, Birmingham

50% of people in the Western world die from atherosclerosis and cardiovascular diseases. A key feature of an atherosclerotic plaque is lipid accumulation in the vessel wall, which leads to a spectrum of clinical problems including heart attacks, strokes, limb loss and death.

50 % of people in the Western world die from atherosclerosis and cardiovascular diseases. A crucial step is the formation of an atherosclerotic plaque, which is an abnormal fatty lesion in the vessel wall. This results from the build-up of harmful lipid particles deposited by inflammatory cells. These cells recognise lipid particles by receptors found on their surface. Studies have shown that an important receptor involved in this process is the LOX-1 receptor. However, little is known about how the LOX-1 receptor takes up lipid particles into cells.

I used genetic engineering to alter amino acids within the LOX-1 receptor. Using special techniques, I studied the ability of the altered LOX-1 receptors to take up lipid particles into cells. I discovered a novel area in the receptor that was responsible for the accumulation of harmful lipids.

My work provides a fundamental understanding of how harmful lipid particles are taken up into cells via this key receptor. This contributes to our understanding of the development of atherosclerotic plaques that predisposes patients to heart attacks, strokes, limb loss and death. Discovery of such novel targets will allow me to develop drugs that affect these key pathways.

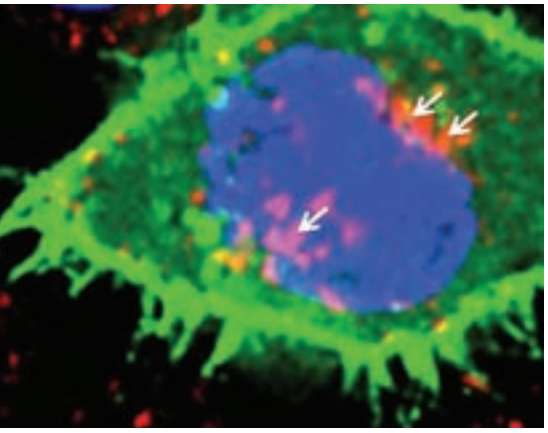
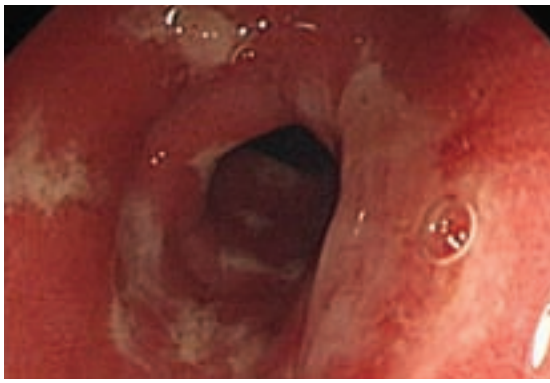


Fig 1 Ravi closing a human chest following open heart surgery
Fig 2 A human cell (green) taking up harmful fat (red, highlighted with arrows) into its the centre (blue)

Metabonomic profiling of pouchitis in the ileoanal reservoir



Pouchitis occurs in around 50% of people with ulcerative colitis who have a pouch and is an important model for studying the causes of inflammatory bowel disease.

Ulcerative colitis is a debilitating inflammatory bowel disease affecting 6,000 new patients in the UK each year and leads to surgical removal of the colon in 30% of sufferers. In order to avoid a permanent stoma, the ileoanal pouch was developed. A pouch is fashioned from small bowel and connected to the anus, allowing stool to be passed normally.

In up to half of patients the pouch becomes inflamed (pouchitis). The exact causes are not known although many believe that an interaction between genetic and environmental factors, including gut bacteria, is responsible. The small bowel is usually not affected by ulcerative colitis; hence pouchitis is an excellent model for studying the potential causes of inflammatory bowel disease.

The study hypothesis was that there are differences in bacterial profiles and associated metabolites in the stool, urine, blood and intestinal tissue of patients with pouchitis and those with healthy pouches. In the first study of its kind, we used high-resolution proton nuclear magnetic resonance (1H-NMR) spectroscopy (technology similar to MRI scanning) to identify hundreds of chemical compounds in each sample. The resulting complex data sets were analysed with pattern recognition techniques. Bacterial profiles were identified using 16S RNA-based DNA fingerprinting techniques.

Patients with pouchitis had lower levels of lactobacilli and enterococci ('friendly' bacteria) in their stool compared to those with healthy pouches. We also found a trend towards reduced faecal levels of short-chain fatty acids (compounds beneficial to intestinal health produced by friendly bacteria) and increased blood levels of alpha-1 acid glycoprotein, an inflammatory protein, in patients with pouchitis. The study showed that reduced numbers of friendly bacteria associated with pouchitis may translate into lower levels of beneficial metabolites produced by these bacteria, thus providing evidence for a mechanism by which alterations in the gut bacteria may contribute to inflammatory bowel disease.

Fig 1 Alex loading a sample on the NMR spectrometer
Fig 2 pouchitis Endoscopic view of pouchitis

MR ALEXANDER CHRISTIAN VON ROON

Fellowship/sponsor
College Research Fellowship

Supervisor
Mr Paris Tekkis, Mr Paraskevas Paraskeva, Miss Sue Clark and Professor Jeremy Nicholson

Site of work
Department of biosurgery and surgical technology, Imperial College London

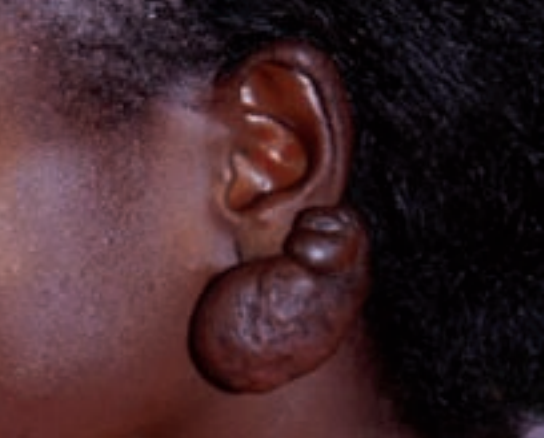
Publications

- von Roon AC, Abecia L, Maronecles M *et al*. Pouchitis is associated with decreased faecal lactobacilli/ enterococci populations. Colorectal Dis 2008; **10 (Suppl 1)**: 37

Presentations

- *Pouchitis is associated with decreased faecal lactobacilli/ enterococci populations*. The Association of Coloproctology of Great Britain and Ireland 2008 annual meeting, Birmingham, 2008

- *Pouchitis is associated with a decrease in faecal lactobacilli/ enterococci populations*. SARS Session, Association of Surgeons in Training conference, Birmingham, 2008



The search for the scarless wound: PAI-1 expression in TGF-beta3 knockout skin wounds

Millions of people are affected by excessive or inappropriate scarring.

MISS WAI-YEE LI

Fellowship/sponsor
Joint College/American College of Surgeons Fellowship

Supervisor
Mark Ferguson and Mamta Shah

Site of work
Childrens Hospital Los Angeles, USA

Presentations

- *Fetal Scarless Healing: The Role of TGF-beta3 and PAI-1*. The 3M/American Wound Healing Foundation award research seminar, 15th annual meeting of the Wound Healing Society, Chicago, USA, 2005

- Li WY, Huang EY, Chong SN *et al. Fetal Scarless Healing: The Role of TGF-β3 and PAI-1*. Surgical Forum, 90th clinical congress of the American College of Surgeons, New Orleans, USA, 2004

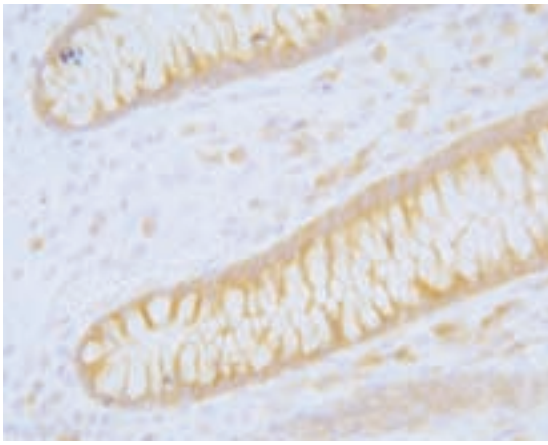
Millions of people are affected by conditions characterised by excessive or inappropriate scarring. Some suffer pain and disfigurement from abnormal scars known as 'keloids,' where scar tissue is continuously formed, often following minor trauma. Others may get internal scarring that can lead to life-threatening conditions such as bowel obstruction, secondary to abdominal adhesions.

Following tissue injury, the process of wound repair and regeneration occurs to restore the integrity and tensile strength of the damaged tissue. Wounds from unborn mammals have the ability to heal without scars, by regeneration of damaged structures, thus offering us the 'holy grail' of wound healing. A better understanding of the events involved in scarless healing may one day enable the medical profession to manipulate the molecular environment of scar-forming adult wounds. The hope would be to reduce or prevent scar formation. The purpose of this study was to investigate the role of the growth factor known as TGF-β3 in fetal scarless healing.

Skin cells, known as fibroblasts, obtained from a genetically engineered animal model lacking the TGF-β3, were found to have an excess production of a tissue scarring factor PAI-1. In addition, these cells were found to have a defect in their ability to re-model scar tissue, a critical determinant in final scarring outcome. These findings allow us a better understanding into the role of TGF-β3 in wound healing. Recombinant TGF-β3 is currently being used in clinical trials for use as an anti-scarring agent in the UK. As a direct result of my involvement in this project, I also studied the role of TGF-β3 in the formation of cleft lip and cleft palate, which rank as two of the commonest congenital human conditions. These two projects form the basis for my PhD thesis.

Fig 1 Keloid scar following ear piercing
Fig 2 Wai-Yee outside The Saban Research Institute, Childrens Hospital Los Angeles, Sunset Boulevard, Los Angeles
Fig 3 Wai-Yee studying a fibrin reverse overlay gel on the light box

Calcium and chemoprevention of colorectal cancer



Colorectal cancer is diagnosed in 36,000 patients per year in the UK and is the second most common cause of cancer-related death.

Dietary factors are implicated in the development of colorectal cancer and high calcium intake is associated with a reduced incidence of this common cancer. Intriguingly, two trials of dietary calcium supplementation have also demonstrated a 20 % reduction in the development of pre-malignant colonic polyps. Understanding how calcium works as a chemo-preventive agent would enable a rational approach to its use in the prevention of colorectal cancer.

This study investigated the mechanism by which calcium works to prevent the development of colorectal tumours and addressed the novel hypothesis that it is via the suppression of serum parathyroid hormone (PTH). Parathyroid hormone is involved in the control of calcium in the blood acting on kidney and bone. The colon is not a classical PTH target organ and in the first part of the study expression of the receptor for parathyroid hormone was demonstrated in normal colon and colonic polyps and cancers.

Gene expression profiling was carried out using microarrays, firstly to identify the genes changed in response to parathyroid hormone in colorectal cancer cell lines. This identified a number of genes modulated by PTH known to be altered during cancer development.

Second, gene expression was studied in rectal biopsies from patients before and after dietary calcium supplementation. A number of genes involved in tumour development changed in response to calcium and PTH was identified as a major determinant of gene expression in normal colon. These results led to a study of patients undergoing screening for colorectal cancer. When this is completed, serum PTH levels will be compared between patients with and without cancer. Understanding the role of PTH and how calcium works to influence the development of colorectal cancer increases the possibility of chemoprevention of colorectal cancer becoming a part of routine clinical practice and a decrease in the incidence of colorectal cancer.

MR MIKE WALKER

Fellowship/sponsor
The Newman Foundation fellowship

Supervisor
Professor Dion Morton

Site of work
University of Birmingham, department of surgery

Fig 1 Mike carrying out endoscopy on a patient to collect samples for the study
Fig 2 Expression of PTHR1, the receptor for parathyroid hormone, in normal colon

Ascending aortic dilatation and its association with abnormal aortic valves

MISS EMMA SUSAN WILTON

Fellowship/sponsor
College Research Fellowship

Supervisor
Miss Marjan Jahangiri

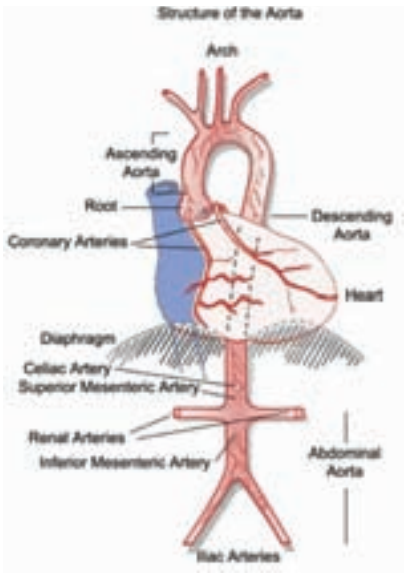
Site of work
St George's, University of London

Publications

- Wilton E, Jahangiri M. Post-stenotic aortic dilatation. *J Cardiothorac Surg* 2006; **1:** 7.
- Nowell J, Wilton E, Markus H, Jahangiri M. Antithrombotic therapy following bioprosthetic aortic valve replacement. *Eur J Cardiothorac Surg* 2007; **31:** 578–85

Presentations

- *Matrix metalloproteinase expression in aortic valve and ascending aorta*. The British Society for Cardiovascular Research and British Atherosclerosis Society joint autumn meeting, Cambridge, September 2006
- *True aneurysm of a bioprosthetic aortic root replacement*. Royal Society of Medicine, London, November 2005



A bicuspid aortic valve is a congenital abnormality affecting 1–2% of the population. It is associated with earlier onset of aortic valve disease, particularly aortic stenosis, which can lead to dilatation of the ascending aorta.

The aortic valve allows blood to flow from the heart into the aorta (the major blood vessel of the body). A congenital abnormality of this valve affects 1–2 % of the population. This abnormality is associated with narrowing of the valve (aortic stenosis) which makes it more difficult for the heart to pump blood into the aorta. Aortic stenosis has also been associated with enlargement of the first part of the aorta. If this enlargement occurs there is a risk that the aorta may rupture and therefore prophylactic replacement of this part of the aorta is indicated. We aimed to determine the association between enlargement of the aorta and congenitally abnormal aortic valves.

Samples of aorta and aortic valve were obtained from 82 patients undergoing heart surgery. We measured levels of specific genes involved in maintaining the integrity of connective tissue within the wall of blood vessels, thereby preventing enlargement. Preoperative and regular post-operative heart scans were performed. No significant difference was seen in the levels of genes we measured between congenitally normal and abnormal aortic valves. However, there was a significant difference seen in a subset of patients with preoperative aortic enlargement.

Previous work studied abdominal aortic enlargement but few studies have analysed gene expression in the first part of the aorta. Most previous research analysed protein levels. Others will hopefully continue to identify further genes involved in aortic enlargement.

We showed that some patients have an underlying preponderance for enlargement of the aorta. Identifying these patients early and modifying expression of the enzymes causing this enlargement may reduce this.

Fig 1 Emma awaiting specimens from theatre
Fig 2 The structure of the aorta (adapted from Cedars-Sinai Health System, USA, www.csmc.edu)

PRIESKEL PRIZE IN ELECTIVE SURGERY

Adherence to post-operative guidelines for the management of women following caesarean section: experience of a rural hospital in Ethiopia

MR DAVID HALL

Medical school
University of Edinburgh

Site of work
Gimbie Adventist Hospital, West Wollega, Ethiopia

Childbirth in rural Ethiopia can be a risky business. Antenatal education is lacking, many women give birth far from hospital and those who do need medical attention often have to travel for several days to reach the nearest labour ward. All this means that Ethiopia has one of the highest maternal mortality rates in Africa. When pregnant women eventually arrive at hospital to give birth their condition is such that a caesarean section is often their only option.

Gimbie Adventist Hospital serves a rural population of around two million people in western Ethiopia. Caesarean sections are the most common operation at this hospital, with roughly 600 a year performed. As a medical student undertaking an elective in general surgery at this hospital, I was interested in looking at the outcome of these operations.

The World Health Organization produces guidelines for the clinical management of women in the developing world following caesarean sections. These guidelines had been approved for use in Gimbie Adventist Hospital and I analysed the extent to which these were followed. I found that there was an 11 % risk of perinatal death following caesarean section at this hospital and that the guidelines were widely ignored. This was most often the case with regard to pain relief and regular monitoring of the health of the new mothers immediately after their operation.

Simple and cheap modifications to care, such as the regular monitoring of blood pressure, temperature and urine output, may improve the maternal mortality rate in this hospital. With the support of the obstetrics department I was able to provide staff training in this. Future UK medical students to the hospital will be able to re-audit whether this has successfully improved outcomes in this hospital.

Fig 1 David in the operating theatre at Gimbie Adventist Hospital prior to assisting on an operation to treat gangrene in an elderly farmer

Fig 2 David at a surgical outreach clinical in a rural Ethiopian village, three hours by jeep and four hours by mule from the hospital

Management of fracture malunion in the developing world

DR JUBIN JOSEPH

Medical school
Green College,
University of Oxford

Site of work
Children's Surgical Centre, Pnomh Penh, Cambodia

My medical elective, as part of my final year of medical school, was spent mostly in Cambodia working in the Children's Surgical Centre (CSC) in Pnomh Penh. The CSC is non-profit corporation recognised as the peak organisation in Cambodia providing a range of specialised rehabilitation surgical services, medical training and support directly to the people of Cambodia.

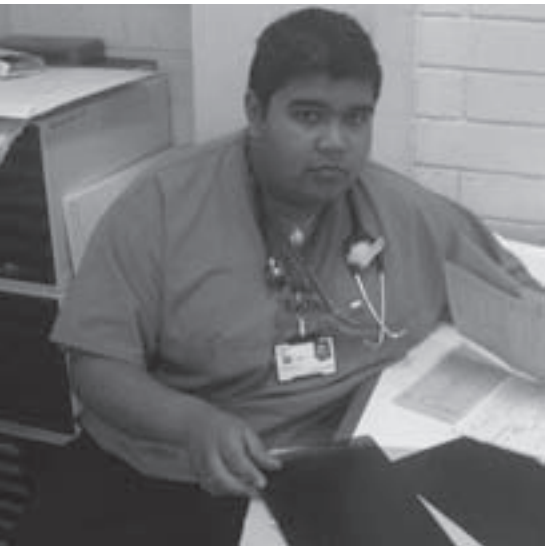
Under the guidance of Dr Jim Gollogy, the CSC provides a wide range of surgery, encompassing facial reconstruction, orthopaedic surgery, eye surgery, and plastic and burn surgery, through which it aims to improve the quality of life for Cambodians. Integral to this mission is a program of training local surgeons and health workers, focusing on the development of sustainable health services.

During my time there I assisted in theatres during cleft lip and palate repairs, cataract surgery and predominantly orthopaedic surgery. This encompassed the revision of painful or disabling amputation stumps from landmine injury, the removal of shrapnel, bullets and other foreign bodies, but concentrated around the correction of fracture malunion. It was the correction of these fractures that I audited, comparing current practice to the evidence available, and I presented findings in a seminar of local surgeons from the district. This process involved educating local surgeons about the process of audit and clinical governance to improve local practice and proved very rewarding.

My elective offered me fantastic insight into the practical realities of surgery in a resource-limited setting, combined with an exposure to a variety of surgical presentations and techniques uncommon at home. The wonderful people, fascinating history and excellent medical training opportunities all mean that I would recommend this placement to other medical students thinking of a surgically orientated elective.

Fig 1 A young boy listening to his own heart for the first time, prior to his clinic appointment
Fig 2 A Buddhist Monk having his blood pressure taken at the triage station of an outreach medical mission

Cardiovascular surgery in Samoa



DR ASHOK KAR

Medical school
Fitzwilliam College, University of Cambridge

Site of work
The National Hospital, Tupua Tamasese Meaole, Apia, Samoa

I hoped to gain an insight into the surgical management of illness relating to cardiovascular disease in the developing world. I was inspired to visit Samoa by the high incidence of both diabetes and rheumatic heart disease in the population.

I was based at the National Hospital, which is the only hospital in Samoa with dedicated operating theatres. I joined the busy surgical team who try to cover all aspects of general surgery along with emergencies, trauma and orthopaedics. A major objective was to develop my core surgical skills and became more confident in the management of acutely ill surgical patients in an environment with limited resources. I actively participated in rounds and on the surgical wards, assisted in a diverse range of cases in the operating room, dealt with referrals including in accident and emergency and helped run outpatient clinics, notably in remote 'district' hospitals.

Numerous patients had surgical complications from poorly controlled diabetes and I conducted an audit, reviewing cases of diabetic foot sepsis and amputation during the previous 12 months and explored how best to reduce morbidity and mortality in surgical practice. In addition I was fortunate to join Dr Mark Hamilton, a visiting vascular surgeon from New Zealand, while he performed arteriovenous fistula formation surgery for patients requiring haemodialysis at the national dialysis centre.

One of the most rewarding aspects of my elective was assisting the team from the New Zealand Good Samaritan Heart Mission to Samoa, who flew in to perform cardiac valvular surgery for patients with rheumatic heart disease. It was an incredible opportunity and I was able to contrast this with previous experiences of cardiac surgery and research at Papworth Hospital in the UK and Stanford Hospital, USA.

Visiting Samoa helped me appreciate the challenges of surgery in the developing world and has been invaluable in encouraging me to pursue a surgical career in the future.

Fig 1 Ashok assisting with an arteriovenous fistula formation
Fig 2 Ashok in outpatient clinic

Surgery in rural Nepal

Health Partnership Nepal (HPN) is the NHS Link between St George's, University of London and Nepal Medical College & Teaching Hospital (NMCTH) in Kathmandu and exists to promote service provision, training, education and research in Nepal. As link coordinator I spent the 2009 elective period at HPN's medical and surgical camps in Nuwakot District in the mid hills north of Kathmandu and at NMCTH in the capital.

80 % of Nepal's surgeons work in the country's large cities while the population is largely rurally based, so surgical services are often delivered to more remote areas through rural surgical camps. HPN's surgical camp took surgeons, anaesthetists, nurses and students from the UK to work alongside their counterparts from NMCTH in providing selected surgical interventions at Trishuli District Hospital, which covers three districts' populations. As well as operating, the HPN team provided training and education to create a sustainable impact after the camp departed.

The HPN team of paediatric and general surgeons assessed patients in hospital clinics and received surgical patients referred from HPN's medical camps in the district. The team were able to operate successfully on all children in the district who required surgery and offer a large number of adults with hernias or hydrocoeles (an abnormal scrotal distension) an operation on site or a referral for surgery at NMCTH.

During my time in Nepal I was able to assist and observe in theatre and also to become involved in preoperative assessment, post-operative care, referral of surgical patients and the logistics of surgical intervention in rural areas. As a result of HPN 2009 we have identified areas of useful research including into the aetiology of hydrocoele in Nuwakot and commenced planning for a national survey of musculoskeletal impairment in Nepal. I return to Nepal next year with an HPN/Feet First training programme in clubfoot management.

MR JAMES MATHESON

Medical school
St George's, University of London

Site of work
Trishuli District Hospital and Nepal Medical College & Teaching Hospital, Kathmandu, Nepal

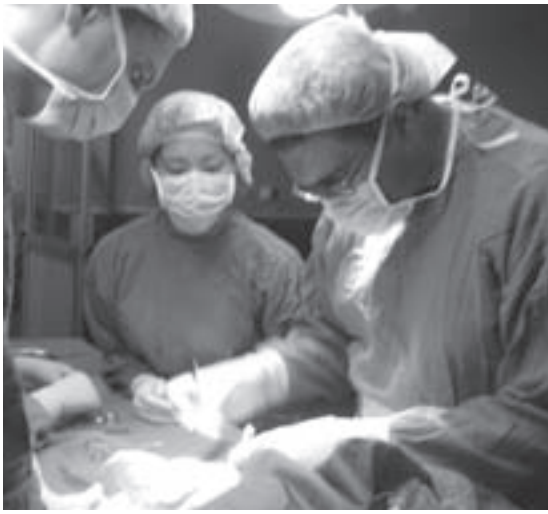


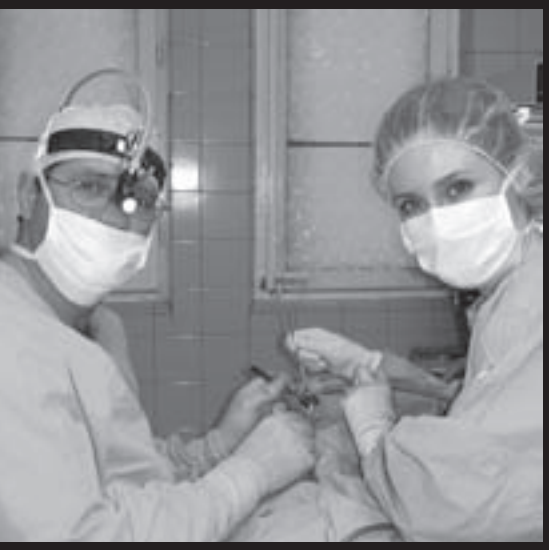
Fig 1 Some of the HPN team at a rural clinic
Fig 2 James in theatre with HPN's paediatric surgeons

Otorhinolaryngology in Hungary

DR TAIJA KRISTIINA NICOLI

Medical school
Barts and The London – Queen Mary's School of Medicine and Dentistry

Site of work
Semmelweis University Hospital, Budapest, Hungary



It was my Finno-Ugrian heritage that initially inspired me to spend my elective in Hungary while learning more about otorhinolaryngology as a specialty. The similarities between our languages are said to date back thousands of years but that is as far as it goes: I could not understand a word of Hungarian, neither did they Finnish. I did, fortunately, learn that ear ('fül'), nose ('orr') and throat ('torok') surgery shares the international language of the scalpel known to all eager surgeon wannabes.

Semmelweis University – home of Hungary's oldest medical school – has a nearly 240-year-old tradition in medical excellence; a perfect setup for an elective, I thought. My aim was to learn to carry out ENT examinations and see whether the field would be something to consider as a career. Besides spending time assisting resident surgeons in theatre I attended audiometry, otoneurology and allergy clinics and learned to carry out basic ENT examinations during my daily visits to the ENT outpatient clinic/ emergency department. The biggest contrast with the UK was the observation that tonsillectomies are still carried out under local anaesthaesia. Even if the latest surgical technology is only found in more affluent countries, its absence is not necessarily a barrier to high standards – a lesson that I quickly learned in the professional atmosphere of Semmelweis.

Looking back at my elective in Budapest my thoughts echo the words of my lecturer: 'Otorhinolaryngology doesn't get the attention it deserves at the medical school.' Hungary, like the UK, is famous for its old scholarly traditions. By selecting a place like Semmelweis as an elective destination medical students not only learn valuable insight into their fields of interest. They too will learn to appreciate the language, the people and the world-famous bath houses during their visit to this historic centre of Europe.

Fig 1 Assisting Dr Rezek in a nose operation
Fig 2 Taija using a drill and sucker in the ear surgery 'practice room'

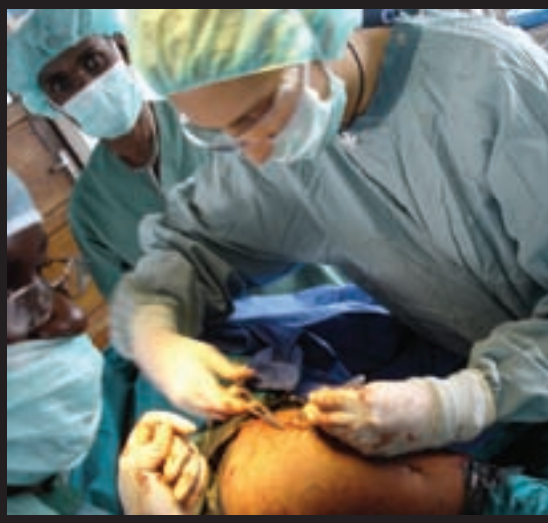
HIV seroprevalence and surgical indications in an African paediatric orthopaedic population

MISS JENNIFER RICHARDSON

Medical school
Imperial College London

Prizes
Winner of PKK Prize

Site of work
Beit CURE Hospital, Lusaka, Zambia



2.5 million children live with HIV. Most of these children live in the developing world, where congenital conditions and orthopaedic trauma are also common. Work continues to make drugs to control HIV available across the world and as a result, more operations are being undertaken on children with chronic HIV infection. Parts of the immune system are involved in the body's response to bone damage and to surgery, and it is still not clear how HIV infection affects these processes.

During my elective in Zambia I spent time working in orthopaedics at the Beit CURE Hospital, Lusaka, and with the FlySpec project in rural areas. I assisted with numerous surgical procedures and progressed to performing my own operations, and undertook a project to estimate the prevalence of HIV in children having orthopaedic surgery at Beit CURE. This information is significant in planning research into the effects of HIV on bone and the best treatment options for patients with HIV.

A retrospective study produced a seroprevalence estimate of 3.05 % among the paediatric orthopaedic patients tested. This was lower than expected and substantially lower than has been reported in general paediatrics in Zambia. Children with chronic immunosuppressive disease are more vulnerable to medical problems that present to general paediatrics, rather than surgical services. Paediatric orthopaedic patients had an average age of 8.33 years, which may represent a 'safe' window between mother-to-child transmission with rapid disease progression and death, and acquisition of the virus through sexual activity. These findings mean that future studies can be planned accordingly.

The elective was a fantastic opportunity to gain surgical experience and to manage a research project in a resource-poor environment. The challenges that arose during the project and clinical work taught me huge amounts about the ingenuity and tenacity needed for successful surgery and research.

Fig 1 Assisting with reconstruction after a snake bite
Fig 2 Closing after excision of tumoural calcinosis

Plastic, orthopaedic and reconstructive surgery at the Children's Surgical Centre, Cambodia

DR RUTH SEAGER

Medical school
King's College London

Site of work
The Children's Surgical Centre and Cambodian Survivor's Charity, Phnom Penh, Cambodia

I spent my elective at the Children's Surgical Centre (CSC) in Phnom Penh. CSC provides much-needed reconstructive and plastic surgery for the poor of Cambodia and people travel many miles to reach them. Many patients have been injured by mines or motorbike accidents and many are suffering from advanced joint tuberculosis.

While based at CSC I assisted with cleft lip/palate repairs and numerous operations for severe limb deformity and osteomielitis. The centre has a busy ophthalmology clinic and undertakes numerous cataract operations and enucleations, with which I also assisted. I gained an insight into how surgical charities work abroad with limited resources and helped to organise a number of equipment donations.

The Acid Survivor's Charity was established in 2006 in response to increasing numbers of acid burn attacks in the country. The horrific practice of 'scaring' a victim with battery acid often kills and maims the most innocent. Many children are orphaned and many people blinded in attacks that very seldom bring the perpetrator to justice. A number of acid burn victims are treated at CSC, with operations including skin grafts and eyelid reconstruction. I was inspired by the unbelievable courage of all the people affected.

During my time at CSC, a group of US marines joined us to set up a field hospital in a temple on the south coast. Each day we saw hundreds of people from throughout the country. Surgical patients were transported back to the capital and CSC, and those with advanced medical illness were referred on for further help.

My time spent at CSC was incredibly rewarding, and a fantastic surgical experience. It has certainly reinforced my long-standing interest in plastic and reconstructive surgery in the developing world. I hope to return to Cambodia one day in a more qualified capacity and would thoroughly recommend CSC to anyone wanting a great hands-on surgical experience in a truly remarkable country.

Fig 1 Ruth examining a patient in Kep, where a primary care facility was set up in a local temple by CSC and the US marines
Fig 2 Ruth assisting with a cleft lip and palate repair, Children's Surgical Centre, Phnom Penh

Caesarean section practices in rural India: an audit

I spent my surgical elective in rural India working with the Swami Vivekananda Youth Movement (SVYM); a charitable organisation that provides healthcare to one of the most neglected sections of Indian society. SVYM serves a practice population of approximately 300,000 throughout the Mysore district situated in the tri-junction of the three south Indian states of Tamil Nadu, Kerala and Karnataka. SVYM runs institution-based and community-based health programmes accessible to both tribal and non-tribal populations.

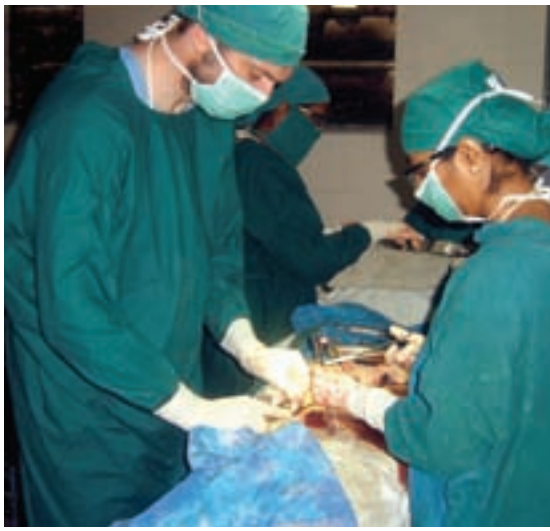
During my time in India my responsibilities were many and varied including: community medicine, paediatrics, obstetrics, gynaecology and surgery. My main role was in theatre, where I had the opportunity to scrub in and assist on many procedures, namely:

- caesarean sections
- hysterectomies
- cataract surgeries
- lower-limb amputations

I also took the opportunity to research Caesarean section (C-section) practices in rural India. Specifically, I compared the performance of the staff at the SVYM versus standards set out in the current National Institute for Health and Clinical Excellence (NICE) guidelines on C-section. The results of this audit were well received by the consultant obstetricians at the SVYM. I made a number of recommendations to improve performance, including:

- designing a number of proformae to ensure clinical information is recorded; and
- procedure improvements based on NICE guidelines, such as offering C-section to all women who are HIV-positive.

This project (plus the necessary theatre time) gave me valuable surgical experience, eg suturing, as well as giving me insight into the value of teamwork in surgery. I look back very fondly on my time in India; I enjoyed the cultural contrast but above all I valued the opportunity to get surgical experience. I believe we all should get experience of medicine and surgery in a developing country.



MR PAUL STEPHENSON

Medical school
School of Medical Education, University of Liverpool

Site of work
Swami Vivekananda Youth Movement, Vivekananda Memorial Hospital, Saragur, Karnataka, India

Fig 1 Paul assisting in theatre
Fig 2 The surgical team

PUMP PRIMING REPORTS

Gene expression and proteomics profiling in cancer diagnostics: a study in colorectal cancer

MR TAN ARULAMPALAM

Fellowship/sponsor
Pump-priming award

Site of work
University of Essex

Publications

- Liao CC, Ward NJ, Marsh S, Norton J. Protein expression profiling of tumour cells in colorectal cancer as an adjunct to disease staging. *Br J Surg* 2007; **94(S3)**: 16-17

- Liao CC, Ward NJ, Wright JM *et al.* Mass spectrometry based proteomic profiling of colo-rectal cancer tissue as a source of biomarker discovery and an adjunct to disease staging. *Br J Surg* 2008; **95 (S6)**: 31

Presentations

- Liao C, Ward N, Arulampalam T *et al. Protein expression profiling in colorectal cancer as an adjunct to disease staging.* Society of Academic Research Surgery, Cambridge, 2008

- Liao C, Ward N, Wright J *et al. Mass spectrometry based proteomic profiling of colorectal cancer tissue as a source of biomarker discovery and an adjunct to disease staging.* 43rd congress of the European Society of Surgical Research, Warsaw, Poland, 2008

Around 100 new cases of colorectal cancer (CRC) are diagnosed each day in the UK.

Early diagnosis of CRC is important in achieving complete cure and reducing the number of patients with advanced-stage disease. Currently there are no non-invasive, blood-based early diagnostic tests with high sensitivity, specificity and positive predictive value that can be satisfactorily used as a routine screening tool. The aim of this study is to assess the use of mass spectrometry-based serum proteomics in the diagnosis of colorectal cancer.

Samples of blood are collected from both normal healthy individuals and patients diagnosed with colorectal cancer prior to surgery. Proteins from the serum samples are purified using hydrophobic interaction chromatography and analysed using mass spectrometry. Preliminary findings with 49 cases of cancer and 90 control sera revealed the specificity of this technique to be between 90 and 100 %. This project hopes to continue following these patients postoperatively to assess their survival/recurrence. It is hoped that this technique may be developed into a potential screening tool for colorectal cancer reducing the need for patients to undergo invasive, expensive tests.

Fig 1 One of Mr Arulampalam's team, Nikhil Pawa, clinical research fellow, spotting samples onto a MALDI target plate
Fig 2 Mr Arulampalam consenting with a patient for surgery

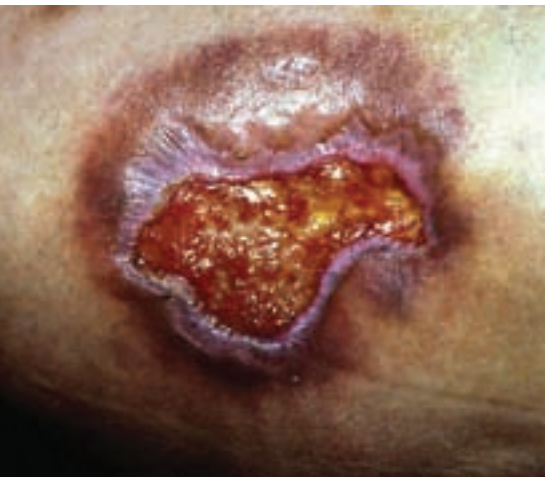
Preclinical gene therapy strategies for Pyoderma gangrenosum

MISS RACHEL HARGEST

Specialty
General surgery

Current position
Senior lecturer/consultant surgeon

Site of work
University Hospital of Wales



***Pyoderma gangrenosum* has no cure and therefore novel therapies need to be explored.**

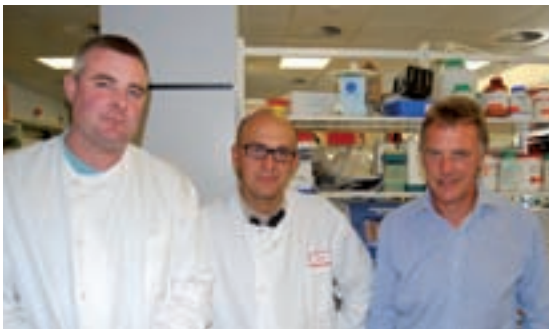
Pyoderma gangrenosum (PG) is a distressing skin condition leading to weeping, painful ulcers in patients who commonly already suffer from inflammatory bowel disease (IBD), rheumatoid arthritis or blood disorders such as leukaemia. An example of a PG skin lesion is shown (Figure 1a). Patients with IBD often require surgery, including the formation of a stoma, and PG has a propensity to occur on the site of scars and stomas (Figure 1b), leading to further suffering. No satisfactory treatment exists for PG and very little research has taken place, apart from trying to treat the underlying disease, which occasionally improves the condition.

This project aims to investigate the growth characteristics of the cells involved in PG and to determine how these are affected by drugs such as steroids and methotrexate. Second, we are investigating the potential for gene therapy as a novel therapy since the lesions of PG are easily accessible to topical treatment and gene delivery to the skin is technically possible. Non-viral gene delivery vectors including liposomes are safe and approved for human use. Therefore we have complexed reporter genes with Lipofectamine™ in order to study gene delivery to fibroblasts and optimise the conditions under which this may be achieved.

The preliminary results have shown that hydrocortisone and methotrexate are powerful growth suppressors and methotrexate also promoted apoptosis of fibroblasts. Second, we have shown that it is possible to introduce reporter genes into fibroblasts safely and to obtain satisfactory levels of gene expression. In collaboration with the Welsh School of Pharmacy we now wish to expand this project in order to identify the most appropriate genes that may have a therapeutic benefit in PG. Second, we are looking at technologies to improve gene transfer to the skin in vivo for the benefit of these patients.

Fig 1 Miss Hargest and research students in laboratory
Fig 2 PG skin lesion

Hypoxia-mediated tumour progression in endocrine neoplasms



One in four patients with a phaeochromocytoma (a rare adrenal tumour) harbours a genetic mutation that favours tumour growth and hormonal secretion.

This report outlines the work undertaken in the first year of a project investigating hypoxia-mediated tumour progression in endocrine neoplasms. The current project expands the vast experience accumulated within the oxygen sensing group led by Professor Peter Rattcliffe and has benefited from conceptual and technical input of one of his postdoctoral fellows, Dr P Pollard. Phaeochromocytomas (PHAEOs) are rare adrenal tumours that can put patients' life at risk because of cardiovascular complications triggered by excessive tumoural secretion of catecholamines, adrenaline (ADR) and noradrenaline (NorA).

An enzyme located within tumour cells, phenylethanolamine N-methyltransferase (PNMT), is responsible for the conversion of NorA into ADR; hence it modulates the clinical symptoms experienced by patients. We found that PNMT is abundant in normal adrenal medulla but rarely expressed in PHAEOs (Figure 1). Only 5/35 tumours analysed showed clusters of PNMT-positive cells. Even though in cell line experiment hypoxia induces PNMT expression, we found no consistent pattern of expression in areas of necrosis/ischaemia within individual tumours.

In collaboration with other research groups we constructed a tissue microarray from 50 PHAEOs. Expression of hypoxia-induced factors (HIF-1, HIF-2) and their downstream mediators is currently being analysed. As in normal tissues, HIF-1 interacts with the von Hippel Lindau (VHL) protein; we aim to explore whether PHAEOs associated with genetic mutations of the VHL gene have a higher expression of hypoxia-induced proliferation. It is yet to be determined which part of this signalling pathway is abnormal in sporadic (non-familial) PHAEOs.

Parallel work in Professor Thakker's laboratory has shown that GATA3, a transcription factor involved in the normal development of parathyroid glands, binds to glial cells missing B transcription factor. This interaction was explored using luciferase reporter assays in HEK-293 cells (paper submitted to *Journal* of *Cell Biology*). In the next stage of this project we will use this luciferase assay to quantify changes in proliferation rates of parathyroid cells exposed to hypoxia.

Fig 1 Radu and Patrick Pollard in the lab
Fig 2 Radu with supervisor, Professor Peter Ratcliffe

MR RADU MIHAI

Specialty
Endocrine/general surgery
Current position
Consultant surgeon, honorary senior clinical lecturer

Site of work
Wellcome Trust Centre for Human Genetics/OCDEM, Churchill Hospital, Oxford

Supervisor
Professor Peter Ratcliffe and Professor Raj Thakkerz

Publications
- Grigorieva IV, Nesbit MA, Stechman MJ *et al*. The GATA3 Transcription Factor Regulates Expression of the Parathyroid-Specific Transcription Factor Glial Cells Missing B (GCMB). Submitted to *J Cell Biol*

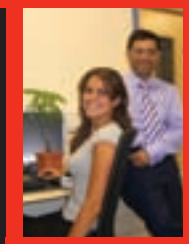
Presentations
- *Hypoxia modulates the catecholamine secretion profile in patients with phaeochromocytomas*. 2009 meeting of the British Association of Endocrine and Thyroid Surgeons, November 2009
- Further results will be submitted for presentation at the 2010 International Symposium on Phaeochromocytoma, Paris, May 2010

HIGHER DEGREES FOR INTERCALATED MEDICAL STUDENTS

Medical students' grants are awarded to students wishing to undertake an intercalated Bachelor of Science degree related to surgery. This has come about in particular from the onset of the Modernising Medical Careers reforms and the demands placed on medical students who wish to consider a career in surgery. Due to the variation in the ways students are funded or not funded for such degrees, students require additional support in areas such as bench fees, consumables or subsistence. Each award is worth up to £5,000.

Medical students

MAY ABBOUDI

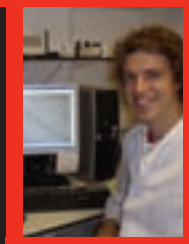


Medical school
Imperial College London

May undertook an evaluation of information transfer and teamwork in patients undergoing gastrointestinal surgery. The aim of this work, undertaken at St Mary's Hospital, Imperial College, London, is to reduce errors in information transfer and thus improve outcomes of patients undergoing major surgery.

May Abboudi and Kamal Nagpal, research fellow, at the Centre for Patient Safety and Service Quality, Imperial College London

CHRIS ALLEN



Medical school
University of Leeds

Chris working in the laboratories of Leeds Institute of Molecular Medicine where he studied new vessel growth in abdominal aortic aneurysms (AAA) to identify the drug process which could stabilise the expansion of AAA and thereby improve the survival of patients.

Chris Allen working in the lab

JUNAID AZAM

Medical school
University of Leeds

Junaid tested several patients in the Academic Unit of Anaesthesia at Leeds General Infirmary to measure their oxygen levels and look at whether exercise testing can be used to predict a patient's quality of life after surgery and how long the recovery time might be.

Junaid assessing a patient in a cardiopulmonary exercise testing laboratory to see if he is fit for surgery

Medical students

EMILY CABOURNE

Medical school
St Mary's Hospital, Paddington

My project has so far provided me with an excellent opportunity to dedicate time and carry out work within a highly academic facility, with cutting-edge experts. With the help of the College grant I was able to move house at the beginning of my project to within walking distance of St Mary's Hospital. This has undoubtedly had a large impact on the efficiency of my project, making it much easier to make full use of my time. With such support I have been able to immerse myself fully in such an important project, which has the potential to make an impact in the academic field of medicine. I am extremely grateful for the recognition of my work that the College has given me and the opportunity that it has given me.

Emily in the lab working on her project

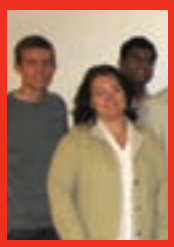
JANE CHEN

Medical school
University of Leicester

The generous grant from the Royal College of Surgeons helped me to undertake a year of basic scientific research looking into the histological appearance of the pancreata obtained from chronic pancreatitic patients undergoing pancreatic islet utotransplantation. During the course of my project, I acquired many laboratory skills and gained valuable insight into the role of academia in modern medicine. Furthermore, the grant supported my attendance at an international conference and a national conference, where I was awarded the prize for best oral presentation.

Jane Chen and Dr Roger James

JOSHUA E ELIAS



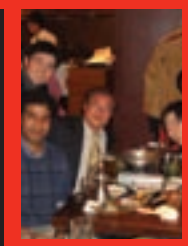
Medical school
University of Leicester

The grant enabled Joshua to attend Society of Academic and Research Surgery (SARS) 2008 conference, then present at SARS 2009, present at the International Student Congress of Medical Sciences in the Netherlands, undertake an international research fellowship in the Netherlands and attend an international transplantation research masterclass with students from all over the world. He was awarded a BSc. degree with first-class honours.

Joshua (far left) at the international research fellowships in the Netherlands

Medical students

JOSEPH GEORGE



Medical school
Imperial College London

Based in the department of orthopaedic and spinal surgery at Tokyo Medical and Dental University, my project investigated bone regeneration using human bone marrow-derived mesenchymal cells. In addition to acquiring basic Japanese, designing sound scientific experiments and learning unfamiliar laboratory techniques, this international research experience has helped me understand the dynamics of the scientific and medical community in the context of a different social and cultural structure.

Joseph (blue jumper) with Professor Shinomiya, Dr Sotome and the research group in Tokyo

JASMINE HO

Medical school
University College London

The award helped fund my iBSc degree in orthopaedic science, where I had the opportunity to work on my own research project in the field of orthopaedics entitled, 'A Retrieval Study: Histomorphological Analysis of Failed Hip Resurfacing Implants'. There were several occasions on which essential equipment for the research broke down and if not for the scholarship, the institution would have not been able to replace it in time for the research's deadline.

Although I did not get enough data for publication, I have been assured that another student will be taking on the project and if this research gets published, the College and I will be acknowledged in the paper.

Jasmine and her supervisor Dr Jia Hua at the Institute of Orthopaedics in Stanmore

CHRIS HONSTVET

Medical school
University of Leeds

This award enabled me to pursue my study of angiogenesis (the growth of new capillary blood vessels in the body) in abdominal aortic aneurysms. My work has been presented at regional and national conferences and I hope to publish a literature review on the topic. My CV has thus been greatly enhanced and has led me to apply for an academic foundation programme.

Chris (at the back) with Professor J Scott, Pam Jones and Chris Allen, another BSc student who continued the project

Medical students

MORTEZA JALALI

Medical school
Leeds Teaching Hospitals NHS Trust

Morteza undertook a Master of Research in medical sciences degree at the University of Manchester, then joined the laboratory of Professor Enrique Amaya at the Healing Foundation Centre in the University of Manchester. Following a six-month research project involving multiple scientific approaches, he was awarded a distinction for his dissertation on embryonic wound healing.

He then commenced an academic foundation training post in the prestigious Leeds Teaching Hospitals NHS Trust and is due to commence a PhD study in surgical research in the summer of 2010.

Morteza Jalali at the lab

KARTIK LOGISHETTY

Medical school
King's College London

The grant was used for Kartik's research in the field of orthopaedics, as part of the surgery and anaesthesia BSc he undertook at Imperial College London.

Working under the tutelage of Professor Justin Cobb, professor of orthopaedics at Charing Cross Hospital, Kartik's research looked at acetabular morphology in femoroacetabular impingement (FAI), an anatomical mismatch between the head of the femur and the acetabulum. Novel 3D analysis of the hip joint has allowed the group to describe the differences between cam and pincer-type FAI, the two forms in which FAI generally occurs. The findings have widespread implications for surgeons practising in this field and will soon be submitted for international presentation and publication.

Professor Justin Cobb, professor of orthopaedics at Charing Cross Hospital, with Kartik Logishetty

RACHEL OLIVER

Medical school
University of Sheffield

Urinary incontinence, a condition associated with bladder overactivity, is a highly prevalent condition often resulting in the need for bladder augmentation. The incorporation of bowel into the bladder is the current gold standard for this procedure; however, it is associated with significant morbidity. Tissue-engineered grafts are a promising alternative but investigation into their mechanical properties is minimal, particularly with regard to the effect of storage. The aim of the study I have been working on is to investigate the effect of storage on the mechanical properties of porcine urinary bladder matrix and its resulting composites.

Rachel with her supervisor, Mr Derek Rosario

Medical students

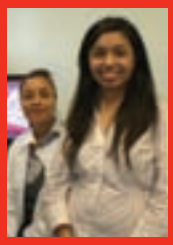
DOMINIC PIMENTA

Medical school
Royal Free Hospital, Hampstead

My project this year is investigating the role of a growth factor, endothelin-1 (ET-1), in the multidrug resistant bladder cancer cell lines. Multidrug resistance eventually develops in a high percentage of cancers and is a major factor in recurrence following cytotoxic chemotherapy. Novel targets such as ET-1 may yield new treatments that can bypass the development of drug resistance. My work is mostly tissue culture proliferation studies using ET-1 and its associated antagonists and agonists, although this has been supplemented with immunohistochemistry and western analysis. Although still ongoing the work has so far produced some interesting results. I hope to continue in the summer with resistant breast cancer cell lines with an additional project paralleling this one, to support my findings.

Dominic with supervisor, Dr Marilena Loizidou

ANIKA PURI



Medical school
University College London Medical School

I am indebted to the Royal College of Surgeons for funding me during this fulfilling year. The BSc not only gained me deeper insight into clinical orthopaedics and orthopaedic science but also allowed me to gain knowledge and equip myself with the skills to be a good, scientifically sound researcher. Such skills are pertinent to any modern-day surgeon. Completing the research project was a particularly fulfilling task and a unique experience, which I will cherish forever.

Anika with her supervisor, Dr Melanie Coathup, at UCL Institute of Orthopaedics and Musculoskeletal science, Stanmore

SIMON ROWLAND

Medical school
Imperial College London

Simon's project was entitled, 'Metabolic changes of bariatric surgery in the resolution of obstructive sleep apnea,' in which individuals suffering from sleep apnea (cessation of breath during sleep) and obesity were recruited from the London Sleep Clinic and the Imperial Weight Centre (Charing Cross Hospital). Their results are allowing them to refine our understanding of how to modify sleep apnea through weight loss, fat distribution changes and gut hormone modulation.

Understanding the mechanisms involved in the resolution of obstructive sleep apnea provides an increased understanding of the development this disorder and will enable the refinement of current procedures in order to improve outcomes in these patients.

Simon with his supervisor, Mr Thanos Athanasiou

LECTURES DELIVERED FROM 2008–2009

Hunterian, Arris and Gale, Arnott, Bradshaw and Robert Jones Lectures delivered from 2008–2009

2008

Hunterian	**Mr James Gossage,** Society of Academic and Research Surgery, 11 January 2008 *Enhancing natural fibrinolysis to premote venous thrombus resolution*
Hunterian	**Mr Michael Lim,** Royal Society of Medicine, 12 March 2008 *Pouch Dysbiosis and Pouch inflammation*
Hunterian	**Dr Walter Chitwood,** SCG of GB and Ireland, 10 March 2008 *Robotic Heart Valve Surgery: A Hunterian experiment to clinical reality*
Hunterian	**Mr Jonathan Earnshaw,** Royal Society of Medicine, 4 April 2008 *Improving the Results of Varicose Vein Surgery*
Hunterian	**Mr Vincent Gnanapragasam,** British Association of Urological Surgeons, Manchester, 27 June 2008 *Multiple levels of regulation control Fibroblast Growth Factor induced tumorigenicity in prostate cancer. Implications for the development of peptide growth factor inhabitors*
Hunterian	**Mr Alex Vary,** Association of Coloproctology, 1 July 2008 *Avastin – improving targeting by typing Vascular Endothelial Growth Factor*
Hunterian	**Mr Patrick Bradley,** British Association of Otorhinolaryngologists, Dublin, 7 July 08 *What to do about salivary diseases: Lessons Learned by a Surgeon*
Hunterian	**Professor Andrew Kingsnorth,** British Hernia Society, 6 October 2008 *Hernia Surgery: From Guidelines to Clinical Practice*
Hunterian	**Mr Raducu Mihai,** British Association of Endocrine and Thyroid Surgeons, France, 9 October 2008 *The calcium sensing receptor: from understanding parathyroid calcium homeostasis to bone metastases*
Hunterian	**Mr Thomas Dehn,** British Society of Gastroenterology Oesophageal Section, 10 November 2008 *Laparoscopic anti reflux surgery – before during and after*

2009

Arnott	**Miss Jennifer Rusby,** British Association of Surgical Oncology, 18 March 2009 *Anatomy of the human nipple*
Hunterian	**Mr Patrick Tansley,** Society for Cardiothoracic Surgery, 22 March 2009 *Reversal of heart failure*
Bradshaw	**Miss Anne Moore**, The Royal College of Surgeons of England, 21 January 2009 *When the air hits your brain; Neurosurgery through the ages*
Hunterian	**Professor Peter Thomson,** British Association of Oral and Maxillofacial Surgeons, 5 June 2009 *Oral preconcert - position, proliferation, prediction and progression*
Arris and Gale	**Mr Michael Jarrett**, The Association of Coloproctology of Great Britain and Ireland, 10 June 2009 *Sacral nerve stimulation for bowel dysfunction*
Hunterian	**David Moffat**, Polizer Society, 5 September 2009 *The evolution of a surgical algorithm to improve five year survival outcomes in squamous cell carcinoma of the temporal bone*
Robert Jones	**Colonel Mike Stewart**, British Association of Oral and Maxillofacial Surgeons, 17 September 2009 *Wounds of mind and body*

FUNDRAISING IN FOCUS

Fundraising in focus

Every year, over six million people undergo surgery in the UK. Surgery remains the mainstay, indeed the only effective treatment for many diseases, including solid cancers of the bowel, breast and lung, diseases causing organ failure (transplantation), victims of trauma, age-related disabilities and disease or injury requiring reconstruction.

With less than 2% of national funding for medical research being applied to surgically based projects there is a desperate need to redress this balance. In 1993 the College launched a programme of support to promote varied and significant surgical research at centres of excellence throughout the country. At the heart of each of the schemes is to bring patient benefit at the bedside and foster excellence in the next generation of surgical research.

Almost 500 research awards have been made since 1993 at a cost of over £21 million. The College receives far more applications than it can support each year and can fund only one in five of the projects it receives.

Charitable support

Surgical research would certainly not have achieved so much were it not for the generous and constant support of our many charitable donors, whose backing has been crucial to the success of this scheme. Put simply, the number of research awards we make is entirely dependent on external sponsorship.

Those who support surgical research do so for a number of reasons. They know that the research will be relevant to patients at the bedside, that only the very best projects are supported and that every gift is allocated directly to the projects and not administration. The wide range of fellowships, grants and prizes available enables donors to select projects that meet their own interests or criteria. We are delighted to name awards eponymously.

The Rosetrees Trust has supported the College's surgical research fellowship scheme since 2000.

'For us the chief difficulty in selecting medical research projects to support is identifying those projects that we feel will lead to a clinical application in a reasonable timeframe. The work of College research fellows is clinically orientated and we have many examples of new treatments and improved practices or techniques that have resulted from their research fellowships.

'We have always been greatly impressed by the very high quality of research and would strongly recommend the scheme to other funders.'

John Samuels, Trust Secretary

Fig 1 Rosetrees trust prize winners and trustees receiving their award at the Diplomates' Ceremony, 7 July 2009

FUNDRAISING IN FOCUS
continued

Joint College/DMT research fellowships

'The Dunhill Medical Trust (DMT) has been working in partnership with the Royal College of Surgeons for over 10 years to support young surgeons in developing vital research skills. Since 2005 these joint College/DMT fellowships have all been focused on diseases of ageing and older people in line with DMT's priority area for support. DMT is delighted to be able to continue this fruitful partnership with the College with the award of five further joint fellowships to be appointed in early 2010.

'This commitment of a further £400,000 over two years has resulted from a recent review of outcomes from previous College/DMT fellowships, which has demonstrated their effectiveness in expanding surgical research capacity and developing surgical careers as well as the potential for evidence gained from the research projects undertaken by College/DMT fellows to develop more appropriate and effective surgical treatments for older people.'
Claire Large, Administrative Director

Charitable events and fundraising

Over the past 18 months the College has launched a UK-wide public events programme from Bournemouth to Birmingham. We have visited over 50 national membership groups to highlight the contribution of academic surgery to improvements in patient care.

FUNDRAISING IN FOCUS
continued

The College would like to acknowledge all those charitable trusts, companies, College fellows and members, and individuals who have supported surgical research at the College including:

Foundations, charitable trusts, corporate donations and individuals

Andrew Anderson Charitable Trust
Ballinger Charitable Trust
Bedfordshire Lodge of Installed Masters, no. 7301
Berkshire Installed Masters Lodge, no. 3684
The Caravan Club (Suffolk Centre)
Clerkenwell Lodge of Installed Masters, no 9628
Croydon Lodge of Achievement
Dunhill Medical Trust
DBP Trust
Enid Linder Foundation
Ethicon UK Ltd
Euclid Lodge of Installed Masters
Family Rich Charities Trust
Fellows fellowship fund – the College is very grateful to its many members and fellows who donate regularly to the fellowship scheme.
Frances and Augustus Newman Foundation
The Family of the late Mr Stefan Galeski FRCS
George Drexler Foundation
Gloucestershire Installed Masters Lodge, no. 7900
Grand Lodge of Freemasons 250th Anniversary Fund
Henry Smith Charity
Herefordshire Masonic Charity Association
Hong Kong Freemasons Overseas Trust
Mrs Bella Hopewell
Kirby Laing Foundation
Lodge of Academe, no. 9337
Lodge of Lu Pan, no. 9387EC
Mr REW Lumley
Oakdale Charitable Trust
Provincial Grand Lodge of Somerset
Roger Vere Foundation
Rosetrees Charitable Trust
Sir Samuel Scott of Yews Charitable Trust
Shears Charitable Trust
Shropshire Installed Masters Lodge, no. 6262
South West Surrey Masters Lodge, no. 5965
Thomas Sivewright Catto Charitable Settlement
Warwickshire Installed Masters Lodge
Wyndham Charitable Trust
WD Macpherson Trust

Joint fellowships

Association of Breast Surgeons, British Association of Surgical Oncology
British Association of Plastic, Reconstructive and Aesthetic Surgeons
British Scoliosis Research Foundation
Cancer Research UK
Core
Society of Academic and Research Surgeons
American College of Surgeons
Arthritis Research Campaign
Botnar family
British Society for Surgery of the Hand
The Healing Foundation
ia – The Ileostomy & Internal Pouch Support Group
Medical Research Council
National Kidney Research Fund
The Restoration of Appearance and Function Trust
Royal Australasian College of Surgeons
The Stroke Association
Welsh Surgical Society

Rosetrees Trust Prizes and awards

Ethicon Foundation Award
Colledge Family Memorial Fellowship Fund
Sir Ratanji Dalal Research Scholarship
MacLoughlin and Morris Scholarship
Norman Capener Travelling Fellowship
The Preiskel Prize and PKK Award
Ronald Raven Barbers' Award
Rosetrees Trust Prize
HJ Windsor Prize

Endowments, restricted and legacy funds

Anderson Reid Fund
Bennett Legacy
Bernhard Baron Fund
Blond McIndoe Fund
Bingley Legacy
Brinsdon Legacy
Buckston Browne Gift
Burghard Bequest
Cameron Legacy
Campbell Legacy
Children with Cancer Research Fund
Mr Dennis Frederick Clark Legacy
LM Coleman Legacy
Collett Legacy
Miss Joan Rosa Cox Legacy
Philip and Lydia Cutner Bequest
Darlow Research Fellowship
Denker Legacy for Research in the UK
Edward Lumley Fund
Ellin Legacy
Mr Geoffrey Gilbert Thurlow Fletcher Legacy
George Clarke Bequest
Gerrish Legacy
Green Legacy
Grimwood Legacy
Mr Irwin Grossman Legacy

FUNDRAISING IN FOCUS
continued

Endowments and legacy funds (continued)

Guyatt Legacy – Sir Alan Parks Research Fellowship
Harold Bridges Bequest
Harry S Morton Fund
Heslop Legacy
Hiller Legacy
James Kent Will Trust
Joers Legacy
Kannaar Legacy
Kathleen Knapp Legacy
Kennard Legacy
DK King Legacy
Knapp Legacy
Laming Evans Research Fund
Lea Thomas Fund
Lillian May Coleman Fund
Louis Alexander Research Fellowship
Maynard Legacy
Muirhead Bequest
Osman Hill Collection and Research
Parks Visitorship
Phillips Legacy
Phillips, PI Legacy
Mrs Barbara Pomfret Legacy
Prophit Trust
Robb Legacy
Seargeant Research Fund
The Dr Shapurji H Modi Memorial ENT Research Fund
Doris Mary Sheppard Legacy
Shortland Legacy
Simpson Legacy
Sir Arthur Sims Fund
Sir John Lang Bequest
Mr Richard John Stafford Legacy
The estate of the late Dr MP Starritt
Mr JG Taylor Legacy
Tudor Edwards Fellowship
Vandervell Research Fund
Watts Legacy
Williams Legacy

For further information on donating to the College's research fellowship scheme, pump-priming awards or prizes, or arranging a local presentation please contact the Development Office at the College: 020 7869 6083, development@rcseng.ac.uk or visit: www.rcseng.ac.uk/surgical_awards_and_grants.

PRIZES AND TRAVELLING AWARDS

Travelling awards

The College is pleased to be able to offer a variety of awards as a result of the generous support of companies and individuals. These awards give surgeons the opportunity to work in an overseas institution to learn more about a particular surgical technique or area. The main benefit of the travelling awards is that the surgeon who benefits can translate the experience and know-how gained during the overseas fellowship to his or her own knowledge base to benefit future patients in this country. The committees that decide the recipients of the travelling awards always include leading surgeons.

The following travel awards are available:

Ethicon Foundation Fund travel award

The Ethicon Foundation Fund was established by the generosity of Ethicon Limited. The fund provides financial assistance towards the cost of the travel to and from a research or training fellowship, thereby promoting international goodwill in surgery. Applicants should be sufficiently advanced in their training to benefit from such an experience or be within one year of their appointment as consultant surgeon.

Recipients October 2007
Mr Jamie Edmund Arbuthnot
Miss Sasha Clare Burn
Miss Sujata De
Mr Harpaul Singh Flora
Mr Vincent Jeyaseelan Gnanapragasam
Mr Shehan Peter Hettiaratchy
Mr Carl Martin Philpott
Mr Alaiyi Frederick West
Mr Stuart Charles Alec Winter

Recipients April 2008
Mr Enoch Francis Akowuah
Mr Kristian Aquilina
Mr Matthew Paul Alexander Clark
Miss Aina Vibeke Hiller Greig
Mr Ian John Hunt
Mr Jee Leem Low
Mr Narain Moorjani
Mr Rami Jean Salib
Mr Rikin Ajaykumar Trivedi
Mr Sanjay Verma

Recipients October 2008
Mr Paul Harnett
Mr John Phillips
Miss Philippa Cheetham
Mr Marc Gladman
Mr Michael Norwood
Mr Shane Lester
Mr Vasu Karri
Mr Robin Elliot

Recipients April 2009
Mr Andrew Cruise
Mr Jimmy Hon
Mr Haris Khwaja
Mr Peter Monksfield
Mr James Webb
Mr Charles Willis-Owen

PRIZES AND TRAVELLING AWARDS
continued

Colledge Family Memorial Fund

The Colledge Family Memorial Travelling Fellowship was established by Miss Cecilia Colledge in 1979 in memory of her father, the distinguished surgeon Lionel Colledge and her brother Maule who died on active service during the Second World War. The fellowship was founded to promote and advance the study and knowledge of surgery, in particular head and neck surgery, for the benefit of patients. Applicants must be senior trainees or new consultants and plan to a study for a period overseas.

Recipients 2008

Mr Christopher Geoffrey Laurence Hobbs
Mr Rami Jean Salib
Mr Stuart Charles Alec Winter

Recipients 2008

Mr David George Grant
Mr Peter Andrew Monksfield
Mr John Stuart Phillips

Sir Ratanji Dalal Research Scholarship

This research scholarship was founded under the will of Sir Ratanji Dinshaw Dalal. It is awarded jointly by The Royal College of Surgeons of England and the Royal College of Physicians of London. Applications are invited for this research scholarship, which is intended to support a project in either tropical surgery or tropical medicine. The scholarship is tenable for one year and is open to all medical practitioners registered in any part of the Commonwealth. It may be held in any institution in Britain or overseas that is approved by The Royal College of Surgeons of England and the Royal College of Physicians of London.

Recipients 2007

Dr Adebolajo Adewunmi Adeyemo
Ms Anna Checkley
Mr Robert Freeman

Norman Capener Travelling Fellowship

This biennial travelling fellowship was founded with funding provided by friends and admirers of the late Norman Capener, a past vice-president and honorary medallist of the College. Applicants should be enrolled for orthopaedic surgical training or have recently completed a course in orthopaedic or hand surgery.

Recipient 2008

Mr Nasir Ali Quraishi

HJ Windsor Prize

The HJ Windsor prize was established in 1975 with a gift from the late Dr HJ Windsor of Brisbane, Australia. The prize is intended to assist in the advancement of surgery by an annual prize for research or educational project in Australia or the British Isles.

Recipients 2008

Mr James Alexander Webb

Mr Marc Anthony Gladman

Ronald Raven Barbers Award

The Ronald Raven Barbers Award was established by the generosity of the Worshipful Company of Barbers (at Ronald Raven's bequest). The award is aimed at assisting trainee surgeons going abroad to develop their individual skills by special education or training of an innovative nature. Particular weight is given to the excellence of the applicant, the innovative qualities of the work to be done and the relevance of such work to the ultimate benefit of patient care.

Recipients 2008

Miss Aina Grieg

Mr Matthew Clark

Recipients 2009

Mr James Gossage

Mr John Philips

The Rosetrees Trust Prize

The College, supported by the Rosetrees Trust, was pleased to announce a new essay prize for surgical research fellows in 2009. The winning essays, discussing the practical application of research for the benefit of patients, were:

First prize Sherif Awad, *Investigating the mechanisms that underlie the development of perioperative insulin resistance – the effects of starvation and carbohydrate loading on mitochondrial function*
Runner-up Antonios Kourliouros, *Inflammation, structural remodelling and the role of statins in atrial fibrillation following cardiac surgery*
Runner-up James Tysome, *Head and neck cancer therapy with* Vaccinia *virus encoding angiogenesis inhibitor*

The College organises regular events for donors to meet researchers and also receive regular feedback on the progress of the research they support. Securing new funds to initiate a research project is extremely difficult and the support of the College has enabled researchers to collect the initial data and evidence necessary to apply to larger national funding bodies. Many fellows are also inspired to continue their research following a fellowship, thereby strengthening the country's academic base and providing the academic surgeons of the future.

CLINICAL EFFECTIVENESS UNIT

Jan van der Meulen, Director

Academic collaboration

The Clinical Effectiveness Unit (CEU) was established in 1998 as an academic collaboration between the College and the health services research unit of the London School of Hygiene and Tropical Medicine. A review of the College's involvement in national clinical audits at that time, led by Professor Sir Richard Doll, had recommended that surgeons leading these audits work closely with academics with expertise in epidemiology, statistics, health services research and social sciences.

Fig 1 Research fellows attending the research methods course on a wintery day outside the College.

The CEU has become a national centre of expertise in methods, organisation and logistics of large-scale studies of the quality of surgical care. It has fostered collaborative links with numerous NHS organisations, the Department of Health (DH) and relevant regulatory bodies.

Currently, the CEU has 15 staff members, seven of whom are academic staff members of the school and four of whom are surgeons. The multidisciplinary character of the CEU is shown by the widely varying backgrounds of its staff (health services research, epidemiology, medical statistics, clinical medicine, public health and social science). The CEU also includes the Centre for Evidence in Transplantation (for more information, see page 83).

Funding

Presently the CEU receives an annual contribution from the College's research funds and the College underwrites four senior academic posts within the school. However, the CEU is working towards being self-funding through obtaining external project grants and contracts. As a result, the financial cost to the College will be limited.

At the heart of NHS policy

Around the same time as the Doll review, the DH published a policy document, *A First Class Service: Quality in the new NHS*, which emphasised the importance of clinical governance as an approach for NHS organisations to improve the quality of their services. One of its key recommendations was that all healthcare providers should participate in national audits appropriate for their specialty. More than a decade later the DH included similar recommendations in their NHS Next Stage Review report, *High Quality Care for All*, which demonstrates the ongoing relevance of the work that the CEU is carrying out.

Epidemiological approach

The CEU has adopted an epidemiological approach for its involvement in national audit projects. An essential element of this approach is that epidemiological methods are being used to generate quantitative evidence on the processes and outcomes of surgical care as well as on their determinants. In simpler words, many projects of the CEU aim to provide a better understanding of why similar patients are treated differently as well as why patients undergoing similar treatments have different outcomes.

Audit and research

Many projects that the CEU carries out straddle clinical audit and research. Clinical audit is a means of quality assessment, focusing on the structure, process and outcome of care. The objective of research on the other hand is to provide answers to questions that directly or indirectly will contribute to defining what is best

Fig 2 Ranjeet Jeevan, Akan Emin, Louise Dickinson and Tom Palser, four research fellows currently attached to the CEU

Fig 3 Enjoying statistics on the research methods course

practice. To put it more simply, research is finding out what you ought to be doing; audit is fi nding out whether you are doing what you ought tobe doing However, most audit projects the CEU is involved in also aim to provide an insight into why variations occur: are you doing what you ought to be doing and if not, why not? This is a very important element of these audit projects because it has the potential to guide activities that aim to address the observed deficiencies in quality of care.

Furthermore, methodological research is required to solve the many methodological challenges that national clinical audits bring about. Minimum datasets need to be developed that are detailed enough to capture all essential clinical information to address the audit questions in a meaningful way but at the same time reduce the burden on health service staff involved in data collection. Questionnaires and data collection forms need to be designed and validated and their feasibility needs to be determined. The development of methods for risk adjustment is essential to make sure that we compare like with like and that we avoid unfair criticism of surgeons and teams who treat more complex cases.

Statistical techniques should be refined and further developed to take the specific clinical context into account. Development of data linkage techniques is needed to allow combining of patient data from different sources, which will reduce the burden of data collection and improve completeness and coverage. Methods of presentation should reflect the needs of the different target audiences, including surgeons, patients, managers and commissioners.

As a result, most projects carried out by the CEU address audit as well as research questions. The research questions add value to the audits by improving the methods that are being used and by guiding their implications and recommendations for clinical practice.

Patient-reported data

Traditionally, national clinical audits only considered information that was reported by clinicians. It is now widely accepted that patients need to be involved as much as possible. Changes in clinical measures based on clinicians' judgements or derived from laboratory or imaging data do not always translate into improvements of patients' symptoms and quality of life. The CEU has led the way in this area. It carried out a pilot study demonstrating the feasibility of collecting patient-reported information after elective surgery. Currently a project is being carried out that pioneers the collection of patient-reported outcomes at national level (Patient Outcomes in Surgery Audit, see below).

CLINICAL EFFECTIVENESS UNIT

Jan van der Meulen, Director continued

Members of the CEU teaching research methods to surgeons from east and southern Africa at the Beit-Cure Hospital, Malawi

Other CEU projects invite patients to answer questions about their experience with the care they have received. These projects can address the accessibility and cleanliness of the facilities but also the information that patients were given about their conditions as well as the extent to which they were involved in making decisions about their treatment.

Patients can also provide valuable information about comorbidity (co-existing conditions that may affect their prognosis) that needs to be taken into account when outcomes are evaluated. Similarly, questions about complications and adverse events may be included in questionnaires given to patients after their treatment. It is often very difficult to obtain this information accurately through other means.

Since 2009, NHS providers in England are required to support the collection of patient reported outcomes after various common elective surgical procedures. About 250,000 patients a year are being invited to complete a questionnaire before and some time after their operation. The CEU plays a leading role in improving methods to compare outcomes reported by patients and in designing summary measures that are meaningful to the public, clinicians and other stakeholders (metrics). This project will also analyse patient-reported outcomes of hip and knee replacement linked to the data that clinicians report to the National Joint Registry.

Hospital episode statistics (HES)

During the last decade administrative data were increasingly being used in audit and research. The HES database contains records with diagnostic and procedure information for all NHS admissions in England. The major advantages of HES are that it provides a national picture and that patients can be followed up over time. Although the quality of the available information has been challenged, the CEU has demonstrated the value of HES in a range of clinical areas.

HES data need to be used judiciously and in the right circumstances. The CEU has built up considerable experience in the use of HES codes to identify particular groups of patients and their condition, the treatments they receive and their outcomes. For example, a coding algorithm was developed and validated to identify patients with comorbid conditions.

The HES database is being used in almost all CEU projects. In some projects HES is used in isolation. However, HES is especially valuable in combination with other data sources. In that way, it may provide the best of both worlds: completeness of coverage of follow-up based on HES and clinical detail derived from clinical data. Ideally HES and clinical data are linked at individual patient level, an approach that is being followed by the National Joint Registry.

Revalidation

In 2009, the CEU started a project that aims to assess the value of administrative data (HES and patient episode data for Wales) for revalidation. Revalidation refers to new requirements for doctors to renew their licence to practise every five years and to complete a process of recertification if they are on the specialist register. HES has the potential to be an important source of information as it is expected that recertification is based as much as possible on clinical outcomes.

This project aims to develop procedure-specific metrics for individual clinicians and multiprofessional teams. In a later stage it will also address disease-specific metrics. The latter will be achieved by linking HES records related to a patient's journey to enable the description of outcomes of a disease pathway.

Information governance

The CEU is continuously strengthening the security of the data it holds. These activities have had an impact on the information governance arrangements within the College as a whole. The College has now completed the Information Governance Statement of Compliance, which implies that it meets all conditions defined by NHS Connecting for Health for handling patient-identifiable data. An action plan has been drawn up that will further strengthen the College's information governance arrangements.

Teaching

Each year, the CEU runs a number of courses for surgeons and other healthcare professionals on statistics, clinical research methods and evidence-based surgery. They use a mixture of teaching methods ranging from plenary lectures to interactive seminars and hands-on computer practicals. Course faculty often includes methodologists recruited from CEU staff as well as senior surgeons with a strong interest in research and audit.

MAJOR PROJECTS IN 2009

National Oesophago-Gastric Cancer Audit

This audit started on 1 October 2006 and is being carried out in partnership with the Association of Upper Gastrointestinal Surgeons, the British Society of Gastroenterology and the National Clinical Audit Support Programme of the Health and Social Care Information Centre. The audit is funded by the Healthcare Quality Improvement Partnership.

National Mastectomy and Breast Reconstruction Audit

This audit is being carried out in partnership with the Association of Breast Surgery at the British Association of Surgical Oncology, the British Association of Plastic, Reconstructive and Aesthetic Surgeons, and the Health and Social Care Information Centre. The audit is funded by the Healthcare Quality Improvement Partnership.

CRANE database

This is a registry of all children born with cleft lips and palates in England, Wales and Northern Ireland, their treatment and the outcomes. The CEU has been the host organisation for this registry since April 2005. CRANE is funded by the NHS specialist commissioners involved in cleft care.

Patient Outcomes in Surgery Audit

The CEU is undertaking an audit of elective surgical treatment (hip and knee replacement, hernia repair and varicose surgery) comparing outcomes reported by patients treated in NHS hospitals, NHS treatment centres, independent sector treatment centres and private hospitals. It focuses on patient-reported outcome measures but also includes surgeon-reported measures. The audit started in October 2007 and is funded by the DH.

UK and Ireland Liver Transplant Audit and the UK Intrathoracic Transplant Audit

These audits are carried out in collaboration with UK Transplant. They accrue and validate data from all transplant centres in the UK and Ireland since 1994 and 1995, respectively. The CEU is responsible for the analysis and interpretation of the data on post-transplant outcome for each participating centre stratified for major risk factors. The audits are funded by the NHS National Commissioning Group for Highly Specialised Services.

The National Joint Registry (NJR)

The CEU supports the data analysis for the NJR's annual reports and performs additional analyses that will have a direct benefit for the NJR in the future.

Referral guidelines for elective surgery

The Realistic Effective Facilitation of Elective Referral (REFER) project aims to develop referral guidelines from primary to secondary care for patients who may need elective surgery. An important question is how patient preferences can be included in these referral guidelines. Guidelines have been developed for patients with osteoarthritis of the knee and lower urinary tract symptoms. The project is funded by the NIHR Service Delivery and Organisation Research and Development Programme.

Value of administrative data for revalidation

This project aims to develop procedure-specific and disease-specific metrics derived from administrative data to assess performance of individual hospitals and/or consultants in the UK and elsewhere. Case studies will be carried out to evaluate the feasibility and validity of these metrics in the areas of ischaemic heart disease, urological malignancies, and peripheral vascular disease. The project is funded by the Academy of Medical Royal Colleges.

CENTRE FOR EVIDENCE IN TRANSPLANTATION

Sir Peter Morris, Director

The Centre for Evidence in Transplantation (CET) is situated in the College's Clinical Effectiveness Unit (CEU). The centre was established in 2005 to evaluate the quality of evidence available in solid organ transplantation. Furthermore, it has been developing an electronic library of all randomised controlled trials in solid organ transplantation, which has now been completed and is available through medical school libraries in England and to members of the European Society for Organ Transplantation (ESOT) as well as to subscribers to the journal, *Transplantation*. Other medical school libraries have purchased it from Ovid, who have been involved in the technical development of the library. We expect its use to spread fairly rapidly over the next few years.

It is often asked why we need an electronic library in transplantation but if we remember that randomised controlled trials (RCTs) and systematic reviews/meta-analyses of RCTs are level-one evidence in any medical discipline then the aim was to develop a very easily searched and comprehensive library that could produce the relevant references in minutes rather than hours. Indeed, the great Archie Cochrane, after whom the Cochrane library is named, predicted the need for specialist/subspecialist libraries of RCTs some 30 years ago: this is the first.

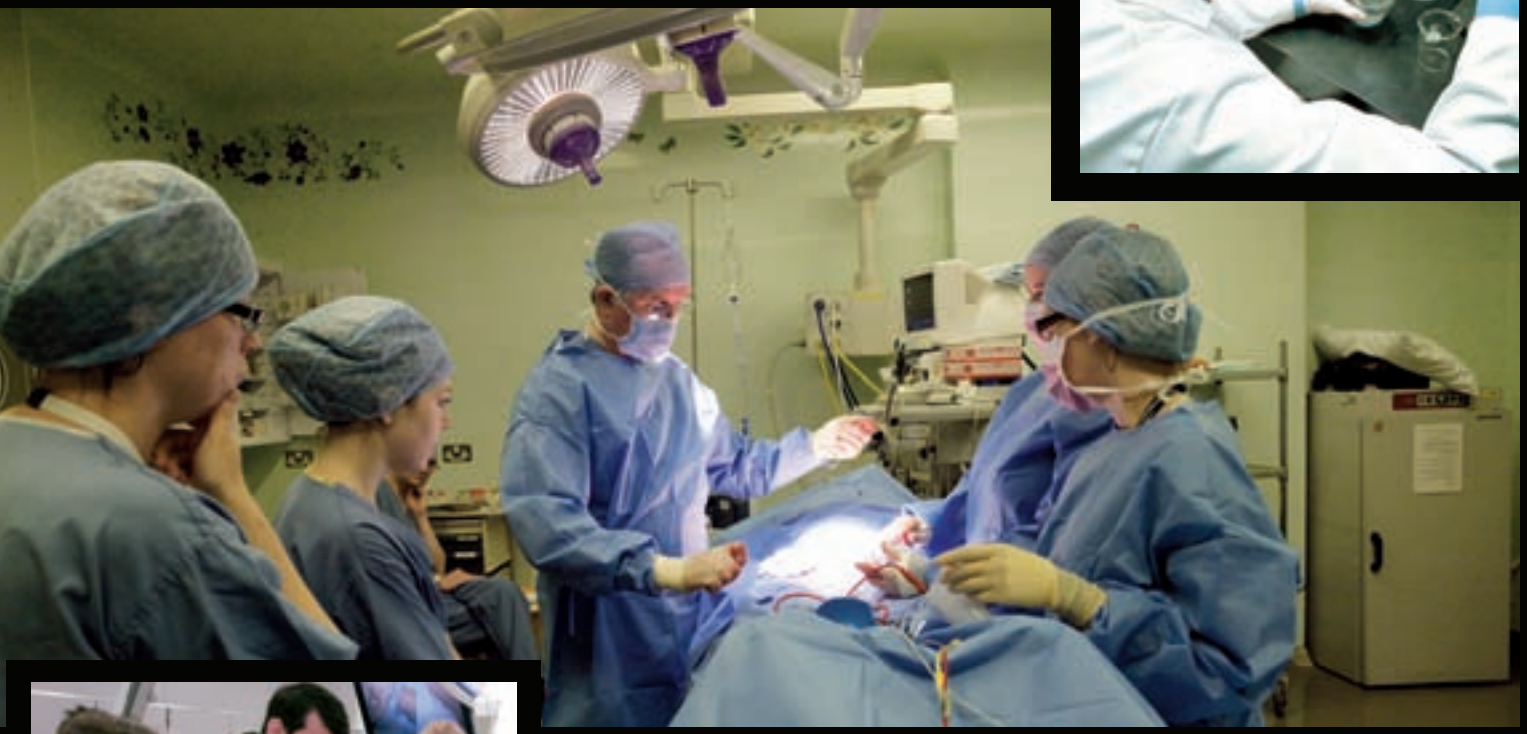
In addition, the CET and the ESOT have begun a collaboration in which it has been agreed that the CET would become the knowledge centre for ESOT with a special emphasis on helping with the design and reporting of RCTs in Europe. One aim of this collaboration is to improve the methodological quality of European trials in organ transplantation by helping the investigators in the early stages of trial design and planning. This of course is not unique to European trials in that the CET has carried out an analysis of all RCTs in organ transplantation published between 2004 and 2006 (around 300), which shows that only one-third of trials reported were of good methodological quality. This does detract from the value of the evidence provided by these poor randomised controlled trials.

There have been a considerable number of publications during the past year. These include, 'The quality or reporting of randomised controlled trials in organ transplantation,' 'Mycophenolate mofetil decreases acute rejection and may improve graft survival, a systematic review,' and publication of the sixth edition of PJ Morris, SJ Knechtle, eds. K*idney Transplantation: Principles and Practice*. Philadelphia: Saunders; 2008. In addition, a comprehensive systematic review of steroid avoidance or withdrawal in organ transplantation has been carried out by Simon Knight, a surgical research fellow. This was part of his thesis, successfully submitted for his MChir degree at University of Cambridge. A presentation of this study at the British Transplantation Society meeting in April was awarded the Medawar prize for the best clinical presentation. In March, together with the CEU, we ran a very successful course here at the College, *Evidence in Transplantation*, for 17 young European transplant clinicians.

Fig 1 Simon with his Medawar prize medal

Further information about the CET is available on our website www.transplantevidence.com

YOU CAN HELP OUR OPERATION BE A SUCCESS



The saving of life, the relief of pain and improved quality of life are ways in which the Royal College of Surgeons is helping millions of people each year. Advances in surgical science are improving the lives of many people through new techniques, training and research.

The College invests in highly focused pioneering research into cancer, heart disease, nerve damage, and diseases in children and the elderly. However, as a registered charity it is not part of the NHS and relies substantially on legacies and donations to continue its activities.

Today's surgeons perform operations barely dreamed of by their predecessors. The achievements of tomorrow's surgeons will depend on the resources to train them and to research new technologies and treatments.

You may have benefited personally from surgery or know someone who has. If you would like to help our operation be a success through a gift or legacy please talk to your solicitor or for more information contact the College:

Development Office
The Royal College of Surgeons of England
35–43 Lincoln's Inn Fields
London WC2A 3PE
telephone: 020 7869 6086
email: development@rcseng.ac.uk
web: www.rcseng.ac.uk/fundraising
Registered charity no. 212808

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