PROCEEDINGS

St Vincent's Clinic

VOLUME 18 No:1 DECEMBER 2010

INSIDE THIS ISSUE ...

ST VINCENT'S CLINIC, SYDNEY VOLUME 18 No:1 DECEMBER 2010

PROCEEDINGS

ST VINCENT'S CLINIC
438 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia
Phone: (02) 8382 6222 Fax: (02) 8382 6402
Email: clinic@stvincents.com.au
Website: www.stvincentsclinic.com.au

EDITORIAL

Dr John O'Neill MD, FRACP

Consultant Neurologist

Editor, Proceedings

This year the Clinic's Sandra David Oration was given by Father Frank Brennan SJ AO, a Director of the St Vincent's Health Australia Board. His lecture explored the ethics and legalities of life and death medical decisions, emphasising both the rights of the patient (patient's autonomy) and the conscience of the doctor. In this 22nd Issue of Proceedings, Father Brennan has provided a summation of his oration which will be of interest to all of those concerned with the ethics of the practice of medicine.

The full text can be accessed via www.eurekastreet.com.au.

In this Issue are five excellent medical articles.

Robotic surgery was first practiced in NSW at St Vincent's Hospital. It is now an integral tool in prosthetic, some cardiac (mainly valvular) and uro-gynaecological surgery. Dr Vince Lamaro was a pioneer of robotic surgery at St Vincent's Hospital and his article explains the advantages and disadvantages of robotic surgery in general, as well as its development and current application in the field of gynaecological surgery.

Dr Reg Lord, upper gastrointestinal surgeon, has written a treatise on Barrett's Oesophagus, a complication of gastro-oesophageal reflux disease and a pre-malignant condition. He explains treatment approaches and the new and effective approach of endoscopic radio-frequency ablation.

Opportunistic infection (usually in immunocompromised hosts) is an increasing problem in hospitals worldwide. Nosocomial (infection acquired within 48 hours of admission to hospital) Candidiasis is a fungal infection which carries a high morbidity and mortality (30% of patients die from the condition). The Australian Candidaemia Study (2001-2004) was a hallmark study which, for the first time, provided accurate nationwide data on the incidence, epidemiology and trends for Candidaemia in the Australian population. The highlights of this study are presented by Associate Professor Debbie Marriott, Microbiologist. In 2008 she was awarded a St Vincent's Clinic Foundation Grant to enable her to study risk factors for Candidaemia in the Intensive Care Units of 5 Sydney hospitals, including St Vincent's. This work is in progress.

Multiple Sclerosis affects 15,000 Australians and is the most common cause of non-traumatic neurological disability in young adults. Whilst in the past this disease was met with relative therapeutic nihilism, better understanding of the immuno-pathogenisis of the condition has led to development of relatively recent and emerging therapies which aim to curtail disease progression. Dr Ian Sutton, an expert in Multiple Sclerosis, takes the reader through these relatively recent and emerging therapies.

Coronary stenting is now the mainstay of "surgical" treatment of ischemic coronary artery disease. Currently potency of coronary stents is dependent upon continued treatment with combination anti-platelet therapy. This becomes a problem when a patient subsequently requires surgery for a separate condition and especially so in the first 12 months after coronary stenting. In their important practical paper, Drs Roy, Roy, Baron and Muller, cardiac interventionists, explain the role of anti-platelet agents in stenting and the risks associated with subsequent cessation of medication. They provide guidelines for management when such a situation arises.

This Issue shows the St Vincent's Clinic Foundation Grants for 2010. Thanks to excellent fiducial management by the Foundation Board and the continuing voluntary work of the Ladies' Committee of St Vincent's Private Hospital and Clinic, the overall value of Grants has continued to increase – $683,000 in 2010 and $740,000 in 2011.

Robotic Gynaecology: A Southern Hemisphere First

Dr Vince P Lamaro

Introduction

St Vincent's Private Hospital had installed NSW first and only da Vinci surgical robot. The hospitals cardiac and urological surgeons had commenced operative programs. No gynaecological unit outside USA and Europe had experience with the da Vinci surgical system.

Our gynaecology team had a broad experience in advanced laparoscopy so in 2006, after extensive evaluation of new technologies for minimally invasive surgery, our surgical team decided to plan, train for and conduct the first robotic gynaecological surgical program in the Southern Hemisphere.

Evolution From Minimally Invasive Surgery To Robotics

Advancements in technology have resulted in improvements to modern-day laparoscopy and options for minimally invasive surgery. Miniaturization of camera technology, high-intensity light sources, an improved range of hand instrumentation and safer tissue cutting and vessel sealing devices have enabled us to perform a greater range of complex surgical cases as "keyhole" procedures.

A prime example is the evolution of hysterectomy from an open abdominal to "keyhole" approach. Approximately 20 years ago, Harry Reich published the first case report of a laparoscopically assisted vaginal hysterectomy. Today our patients commonly have the option of total laparoscopic hysterectomy. Studies have clearly shown that laparoscopic surgery allows faster recovery with shorter hospitalization, improved cosmesis, decreased blood loss, and less postoperative pain. Despite the technologic advancements and proven benefits seen with hysterectomy, other complex procedures (such as the management of advanced colorectal endometriosis and procedures that require extensive suturing such as myomectomy and pelvic floor reconstruction) are typically still managed by laparotomy.

One major obstacle to the more widespread acceptance and application of minimally invasive surgical

Dr Vince P Lamaro B Med FRANCOG
Conjoint Senior Lecturer UNSW,
Director, Institute of MI Surgery,
St Vincent's Campus,
Director of Clinical Training,
St Vincent's Campus

techniques to gynecologic surgery has been the steep learning curve for surgeons and longer operative times associated with many of these advanced procedures. Other limitations encountered with conventional laparoscopy include counterintuitive hand movements, two-dimensional visualization and limited degrees of instrument motion within the body as well as ergonomic difficulty and tremor amplification. Overall, it is unclear whether the difficulty in training surgeons to feel comfortable with laparoscopic surgery is due to trainees and surgeons having an inadequate volume of surgical cases to maintain a comfort level with this technology and transcend the learning curve or whether there are inherent limitations of laparoscopy that make gynecologic surgeons choose other routes of surgery.

In an attempt to overcome the challenges of prolonged training time and ergonomics in laparoscopic surgery, robotic procedures have been recently developed to perform many of the more complex surgeries we conduct in gynaecology. Robotic surgery carries with it the potential to transform laparoscopic surgery by providing, for the first time, instruments with distal ends that mimic the intricate movements of the human hand while at the same time providing the surgeon with a high-definition, three-dimensional view of the operative field. As this technology grows and develops, the hope is that further refinement and improvements will allow for even more precise and even less invasive surgical options beyond laparoscopy and the current forms of surgical robots.

The Da Vinci Surgical System is the only current robotic surgical platform internationally utilized for a range of surgical specialties. St Vincent's Private operates New South Wales only da Vinci System. It comprises three components: a surgeon's console, a patient-side robotic cart with four arms manipulated by the surgeon (one to control the camera and three to manipulate instruments), and a high-definition 3D vision system. Articulating surgical instruments are mounted on the robotic arms which are introduced into the body through cannulas. The device senses the surgeon's hand movements and translates them electronically into scaled-down micro-movements to manipulate the tiny multi-articulated instruments. It also detects and filters out any tremors in the surgeon's hand movements, so that they are not duplicated robotically. The dual cameras used in the system provides a true stereoscopic 3-D picture transmitted to a surgeon's console. **(Figures 1a & 1b)**

Figure 1a: *Surgeons Console (left), da Vinci Robot arms in patient (centre) and Vision Cart (right)*

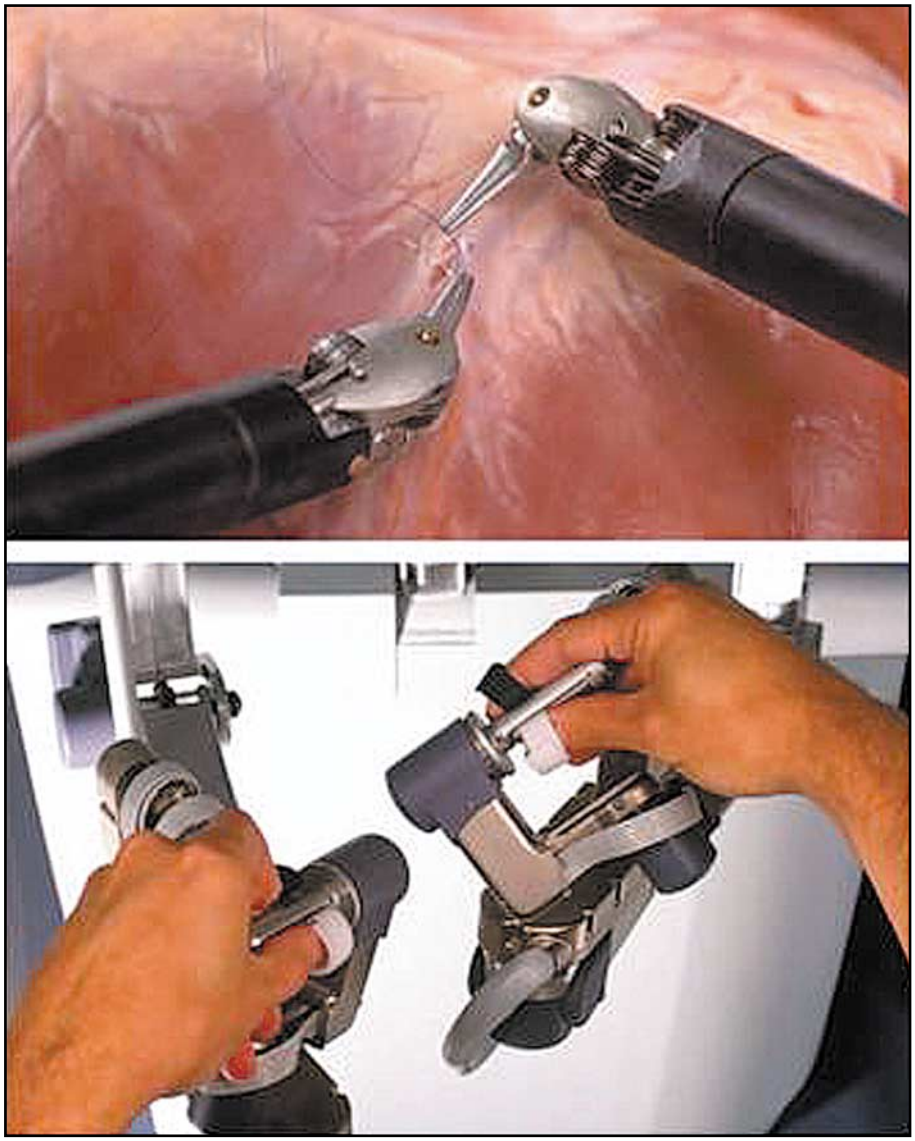


Figure 1b: *Surgeon's wrist and finger movements are translated to the articulated instruments attached to robotic arms within the patient.*

Advantages of Robotic Surgery

Robotic surgery or, more correctly, robotic assisted laparoscopic surgery may have various advantages over laparoscopy. Like laparoscopy, robotic surgery has very clear and proven benefits over more traditional types of surgery for the appropriate case type and surgeon.

The design and technology advantages include a three-dimensional vision system, wristed instrumentation and ergonomic positioning for the surgeon while performing surgical procedures.

The da Vinci robot employs two magnifying, wide-angle cameras that when aligned provide three-dimensional vision to the console surgeon with an available high-definition vision system. The benefit here is with difficult tissue planes, complex anatomy and very prolonged cases.

Wristed instrumentation allows the gynecologic surgeon to obtain the exact instrument angle available at laparotomy. This also eliminates the fulcrum effect that is present with laparoscopy where surgeons need to move their hand toward the patient's left if they want the instrument moved to the patient's right (one of laparoscopy's great training hurdles). With robotic surgery, the movements are natural and surgeons move their hands in whichever direction they want the instruments to move. The "wristed" instrumentation affords greater dexterity and provides seven degrees of freedom, similar to the human hand. Three degrees are provided by the robotic arms attached to the abdominal wall trocars (insertion, pitch, yaw) and four degrees result from the "wristed" instruments (pitch, yaw, roll, and grip).

Fatigue and physical discomfort can become limitations during any surgical procedure. During laparoscopy, surgeons are often contorted to successfully complete the surgical procedure because they need to reach over the patient's abdomen to manipulate the hand controls on the laparoscopic instruments. With robotic surgery, the surgeon sits comfortably at the surgical console from the vantage point of standing at the patient's head and manipulates the hand controls and foot pedals while in an ergonomic position. This may serve to reduce fatigue and discomfort during complex surgical procedures.

Finally a major and in my view "the major" benefit is the training ability and learning curve. Training a surgeon in advanced laparoscopy has always required a dedicated program and extensive case numbers and time. The intuitive nature of the da Vinci allows rapid progression from simplistic tasks to complex surgical procedures.

Disadvantages of Robotic Surgery

The disadvantages widely accepted relate to cost, size and relatively limited instrumentation.

The purchase cost and annual maintenance of robotic equipment is exceedingly expensive. This relates to the effective monopoly held by the da Vinci as only one surgical robotic platform currently exists. This is a short term issue with such a rapidly developing technology. For its job, the robot size is enormous. Positioning and intra-operative patient access – particularly vaginal access – is limited. It is however reminiscent of the original IBM computers that would fill a room – now replaced with laptop computers. The evolution in miniaturisation will be essential to its wider use. As the instruments are proprietary, the huge range we currently enjoy for laparoscopy is not available. Again this is an evolutionary stage. While training time is reduced due to the intuitive nature of robotics, the available training site

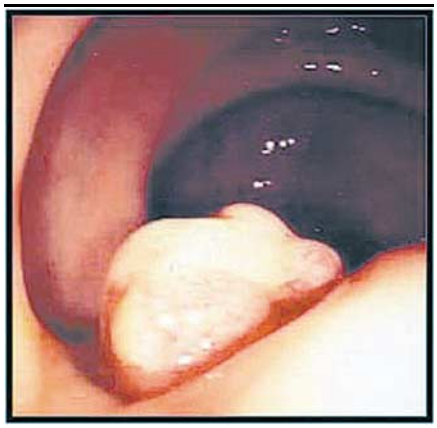


Figure 2a: *Posterior rectal wall endometriosis colonoscopic view.*

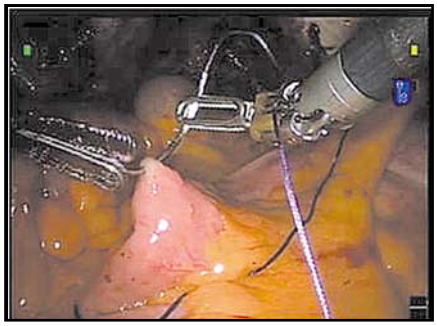


Figure 2b: *Robotic "wristed" instruments facilitate bowel repair.*

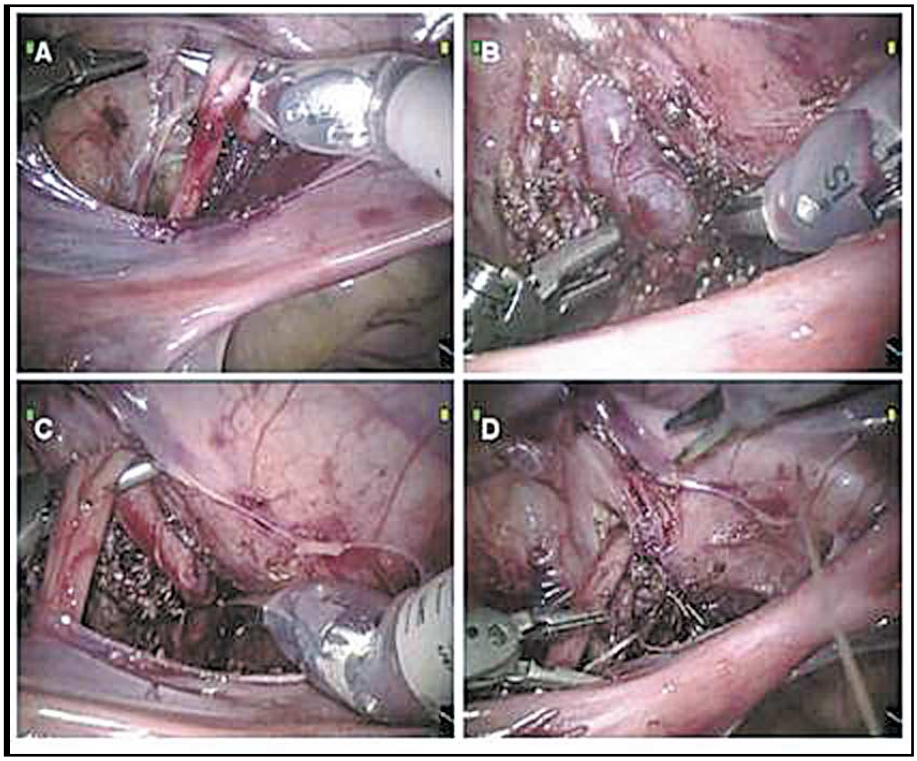


Figure 2c: *Ureteric dissection greatly aided by 3D optics and multi-articulated robotic instrumentation.*

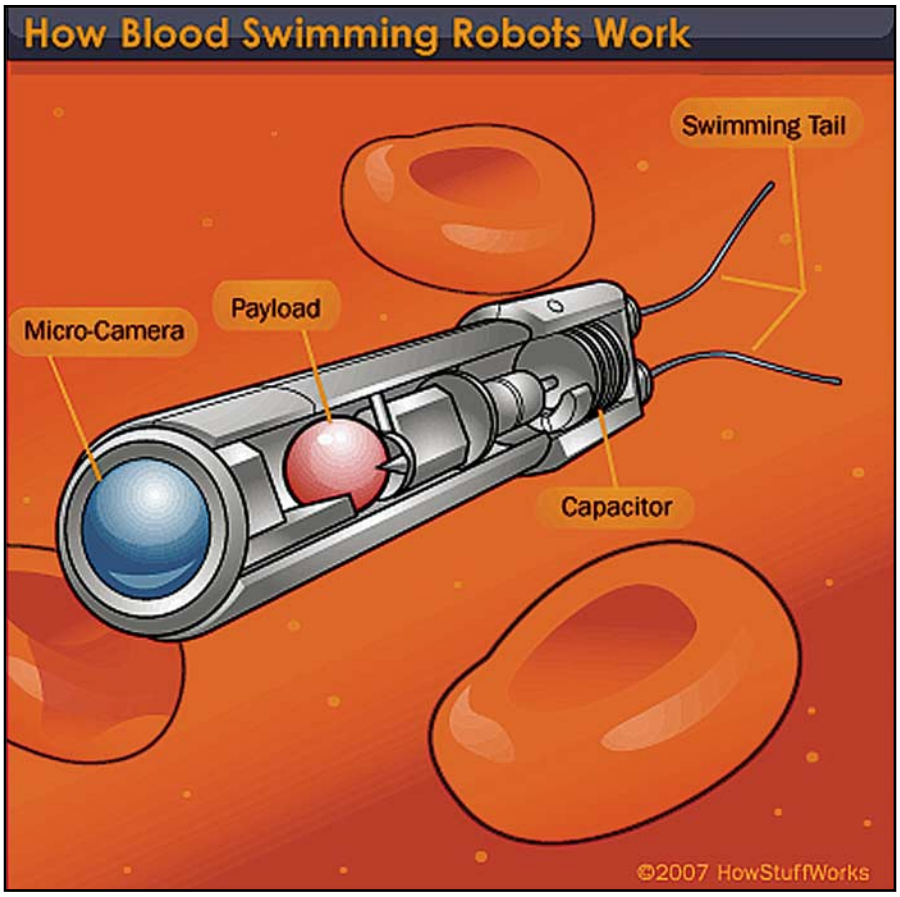


Figure 3: *Schematic for Nano-Robotic device.*

numbers currently limit training and mentoring abilities, St Vincent's Private being the only robotic training centre in NSW.

Further disadvantages generally reported by surgeons currently performing advanced laparoscopy include longer robotic case time, limitations to some procedures requiring haptic (tactile) feedback and the larger port number and diameter.

Robotics in Gynaecology

Historically, gynaecological surgery drove the major progress in technological and training developments for advanced laparoscopy available today. While gynaecology in the USA is a major driver for robotic research and development, the number of well trained laparoscopic surgeons in Australia has so far slowed its progress in this specialty here. We have been fortunate to have evaluated the current technology to perform all procedure types we currently conduct by laparoscopic surgery.

The surgical advantages and improved possibilities we currently see for our patients, accepting limitations mentioned above, relate to procedures involving :

- extensive use of microsurgical suturing;
- reproductive tubal surgery;
- the very prolonged case – myomectomy, rectal and ureteric endometriosis; and
- the ergonomically challenging case-bowel and ureteric re-anastomosis.

Figure 2 (a-c) demonstrates the robotic surgical technique in dealing with advanced stage colorectal and ureteric endometriosis. These represent the most complex cases and potentially the highest morbidity. Full thickness mucosal disease requires complete excision and re-anastomosis of the resected segment of bowel or ureter. This has always been a complex procedure to achieve laparoscopically even when involving a multidisciplinary team. Again it is felt that the ergonomic advantage and articulation of the "wristed" robotic instruments allow a more efficient and correct surgical result. Working at extreme angles such as low posterior rectal wall and lateral ureter is greatly facilitated by this technology as seen in these figures.

Conclusions

The da Vinci surgical robot has proven to be an exciting piece of technology. In its current form, its broad role in gynaecology with our strong history of advanced laparoscopy remains questionable, the major limitations being cost and size. Its importance in redefining a "new" learning curve for surgical training in minimally invasive surgery cannot be understated.

The natural progression of this technology will be toward a more miniaturized, agile, delicate and cheaper technology making this type of surgery a benchmark internationally rather than a curious luxury.

So what about the future?

When I wrote my first article for St Vincent's Clinic on minimally invasive surgery, the "future" discussion surrounded potentials in robotic surgery and the ongoing developments and possibilities. Many of these were in design stages and are now in daily surgical use. The most visible technology on the horizon will be that associated with great improvements in current day robotic design. These include: miniaturization of the robot with simpler "attachment" to the patient; refinement and broader range of instrumentation; engineering haptics or a "sense of touch and position" into the surgeons console allowing more accurate feedback during surgery; and programming a robot for preplanned surgery based on computerized algorithms generated by pre-operative imaging devices.

A future objective of robotic surgery is to enable tele-surgery. ie: the ability to operate on a patient in a remote location. This is now becoming feasible.

In concept stage are miniature robotics or **nanorobotics** involving tiny, almost molecule sized surgical and medical delivery devices that interact with discrete cells to achieve their outcomes **(Figure 3)**.

Dr Reginald V.N. Lord

Endocopic Radiofrequency Ablation for Barrett's Oesophagus

Barrett's oesophagus is the condition in which the normal squamous epithelium of the distal oesophagus is replaced by a metaplastic columnar epithelium which on microscopic examination has intestinal metaplasia with mucin-containing goblet cells **(Figure 1)**. Estimates of the prevalence of Barrett's oesophagus vary but the most accurate data suggest a population prevalence of approximately 1.6 per cent overall and five per cent in white males. An Australian study found that the frequency of diagnosis of Barrett's oesophagus has increased from 2.9 to 18.9 per 1000 endoscopies between 1992 and 2002.

Barrett's oesophagus arises as a complication of gastroesophageal reflux disease. Most patients with Barrett's have a hiatus hernia, a defective lower oesophageal sphincter, and reflux of both gastric acid and weakly acidic duodenal fluid. The disease has a strong male predominance and increases with age. There is an inconsistent association with obesity as measured by body mass index (BMI) but strong associations with measures of central adiposity such as

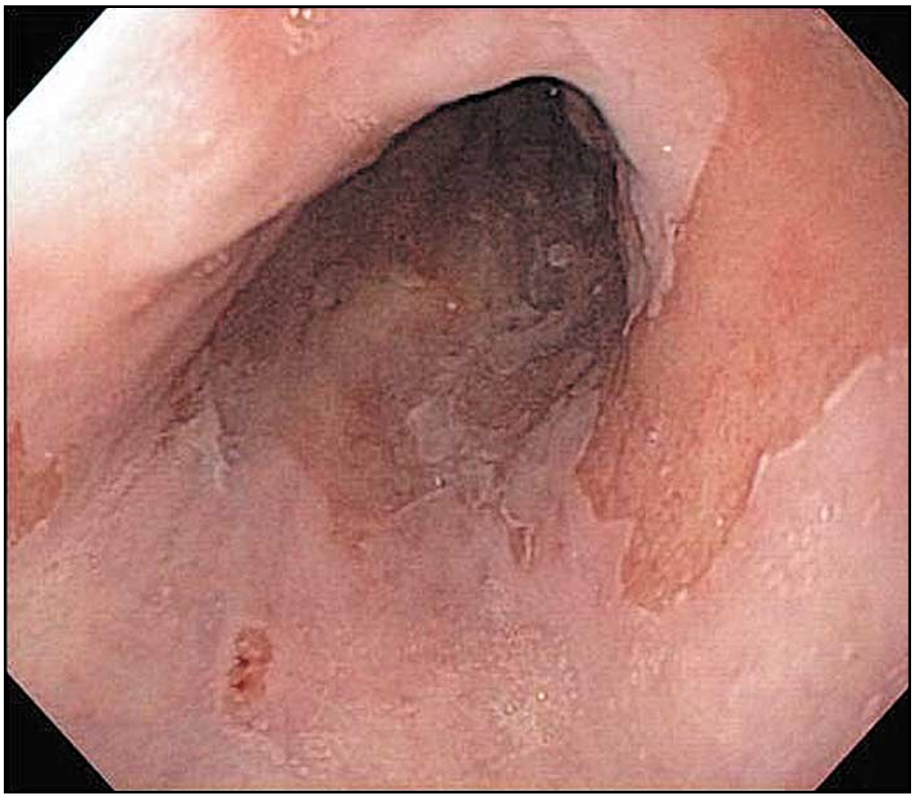


Figure 1: *Endoscopic view of areas of Barrett's oesophagus before treatment*

Reginald V. N. Lord MD FRACS,
Angelique Levert-Mignon BSc,
Sebastian Kwon MBBS FRACS,
Antony Wettstein MBBS FRACP

Diagnostic Endoscopy Centre,
St. Vincent's Clinic, and
St. Vincent's Gastroesophageal
Cancer Research Laboratory,
St. Vincent's Centre for Applied
Medical Research, Darlinghurst

waist circumference and waist-hip ratio. This indicates that visceral fat is implicated in the pathogenesis of Barrett's oesophagus and may partly explain the male predominance, as males tend to have a more central fat distribution than females. Tobacco smoking is also a risk factor. There is an inverse association between gastric *Helicobacter pylori* infection and both Barrett's oesophagus and oesophageal adenocarcinoma.

Barrett's oesophagus is the main predisposing factor for adenocarcinoma of the oesophagus and gastroesophageal junction. The risk of developing adenocarcinoma is approximately 0.5 per cent per year for a patient with Barrett's oesophagus without dysplasia, rising to approximately 10-20 per cent per year for those with high grade dysplasia. In Australia the incidence of oesophageal adenocarcinoma is increasing faster than that of any other cancer.

Endoscopic radiofrequency ablation

Endoscopic techniques are increasingly being used to remove part or all of the Barrett's oesophagus segment, after which there is replacement by squamous epithelium. Standard treatments include endoscopic mucosal resection and argon plasma coagulation. Endoscopic mucosal resection is particularly useful for removing lesions such as nodules and sometimes flat Barrett's mucosa. In patients with high grade dysplasia or intramucosal cancer it can be used for treatment as well as for evaluating depth of disease. If invasive cancer is detected by mucosal resection or other investigations, endoscopic therapy is not considered a curative therapeutic option. Another treatment, photodynamic therapy, is no longer used in this country.

Radiofrequency ablation (RFA) is a relatively new treatment for the removal of Barrett's mucosa. Using either a balloon catheter (circumferential HALO^{360}) or focal flat plate catheter (HALO^{90}) system, radiofrequency energy is delivered to the mucosa to destroy it **(Figure 2)**. The ablated epithelium is then removed by the clinician using endoscopic irrigation, suction, and light pressure. The depth of ablation is less than one millimetre and stricture formation is thus very uncommon.

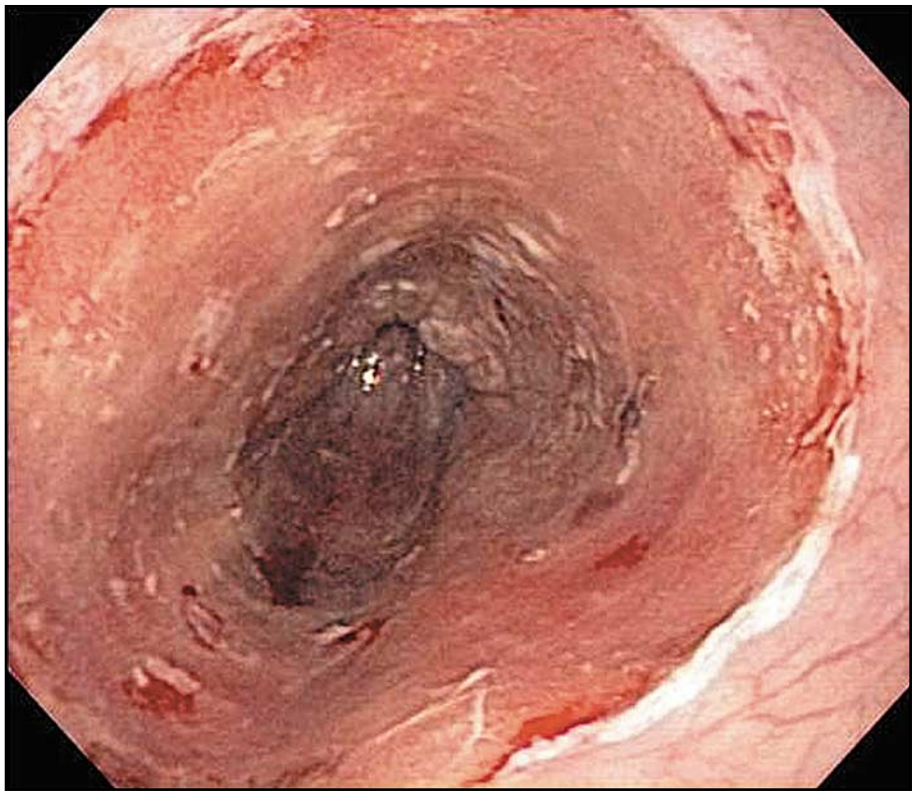


Figure 2: *Endoscopic appearance of the oesophagus immediately after radiofrequency ablation.*

Endoscopic RFA is performed under sedation as an outpatient procedure. Safety has been adequately demonstrated, with only minor complications. This contrasts markedly with the previous standard treatment for Barrett's oesophagus with high grade dysplasia or intramucosal cancer, namely oesophagectomy. The introduction of RFA has resulted in a change in the treatment paradigm: first line therapy for Barrett's high grade dysplasia is now endoscopic RFA with or without endoscopic mucosal therapy, with oesophagectomy reserved for second line therapy.

Publications on RFA have mostly been case series, which report excellent efficacy but are low quality studies. Shaheen et al.[1] reported the one randomised controlled trial of radiofrequency ablation versus a sham procedure in 127 patients with low grade or high grade dysplasia. Of the 127 recruited patients, 117 completed treatment as per the protocol. The study methods included concealed allocation with a 2:1 treatment:sham ratio, stratified randomisation according to the grade of dysplasia and length of Barrett's oesophagus, independent review of baseline pathology by two pathologists, and blinded analysis by an independent statistician.

Complete eradication of Barrett's oesophagus in all ablation patients, assessed on an intention-to-treat basis, was 77 per cent (65/84), compared to 2 per cent (1/43) in the control group. At 12 months follow up the incidence of subsquamous Barrett's oesophagus was 5 per cent (4/84) for the ablation group and 40 per cent (17/43) in the control group. In addition, disease progression (for all levels of dysplasia) was significantly lower (four per cent) in the ablation group compared with 16 per cent in the control group. For patients with high grade dysplasia the rate of complete eradication of all Barrett's oesophagus was higher (74 per cent) in the intervention group compared to the control group (0 per cent). Results were similar for patients with low grade dysplasia and RFA outcomes were superior when analysed according to actual treatment received rather than by intention-to-treat. A significant reduction in new adenocarcinoma cases was found, but larger studies with longer follow-up are needed to confirm this as well as the other study findings.

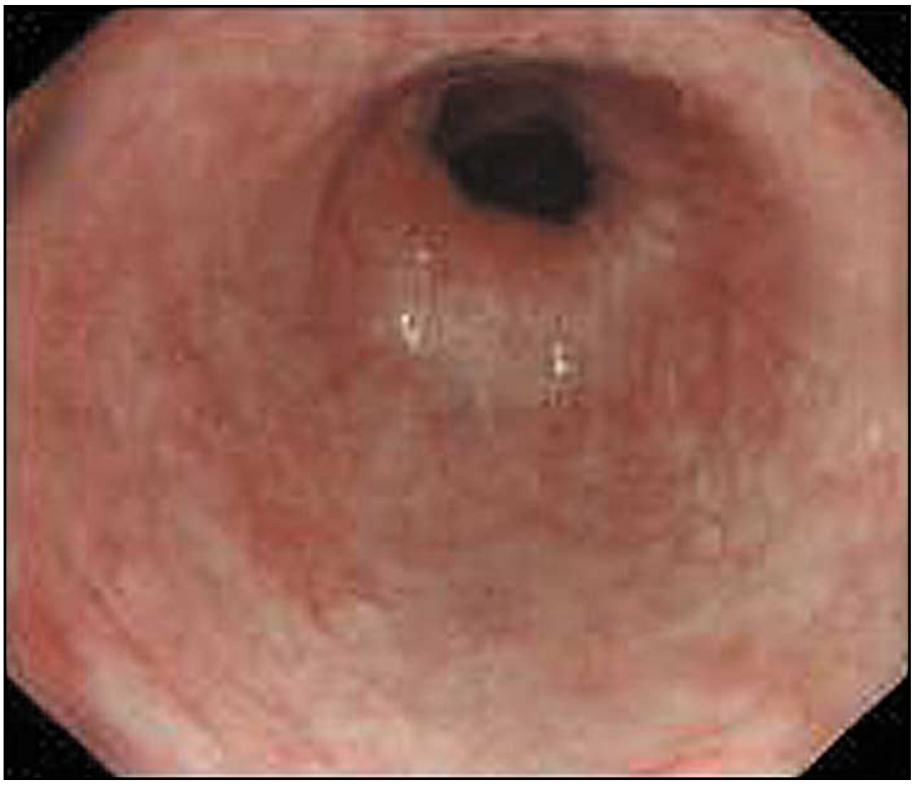


Figure 3: *Post-RFA: normal appearing squamous mucosa after re-epithelialisation*

Endoscopic radiofrequency ablation at St. Vincent's Clinic with illustrative case report

The first radiofrequency ablation procedures for Barrett's oesophagus in Australia were performed at St. Vincent's Clinic in the Diagnostic Endoscopy Centre in September 2007.

The first patient was a woman with longstanding systemic sclerosis and scleroderma oesophagus. As is typical of this disease, she had a hypotensive lower oesophageal sphincter and poor oesophageal motility, resulting in severe gastroesophageal reflux that was not cleared effectively because of the lack of peristaltic contractions in the tubular oesophagus. Medical therapy with acid suppression therapy using proton pump inhibitor (PPI) drugs and laparoscopic antireflux surgery are significantly less effective in patients with scleroderma oesophagus compared to other patients with reflux disease. Operative construction of a lower oesophageal antireflux barrier can result in unacceptable dysphagia, as the hypomotile oesophagus is unable to overcome the high pressure zone of the fundoplication. Especially because of this lack of other therapeutic options, when this patient developed persistent low grade dyplasia within her Barrett's segment, the ideal treatment to prevent further Barrett's progression to high grade dysplasia or adenocarcinoma was to ablate the Barrett's mucosa. Only one endoscopic RFA treatment was required and at three years' follow-up she has no Barrett's oesophagus on endoscopy.

We have subsequently successfully treated more than 10 patients using this therapy at St. Vincent's Clinic.

Conclusions and ongoing studies

Endoscopic radiofrequency ablation is a highly promising therapeutic option for patients with Barrett's oesophagus. RFA is especially valuable for those with high grade dysplasia or early intramucosal cancer, in whom this endoscopic outpatient treatment seems likely to be curative in most patients, avoiding the need for an oesophagectomy. The effectiveness of RFA is being investigated in a multicentre Australian study. Preliminary results from the St. Vincent's Gastroesophageal Cancer Research Laboratory indicate that the new squamous epithelium that replaces the Barrett's oesophagus **(Figure 3)** has a genetic profile similar to normal squamous epithelium from patients who have never had Barrett's oesophagus. The study also shows, however, that any residual Barrett's has the same genetic alterations as untreated Barrett's oesophagus, indicating that the aim of therapy should be complete ablation of all the Barrett's segment.

References

1. **Shaheen NJ, Sharma P, Overholt BF, et al.** Radiofrequency ablation in Barrett's esophagus with dysplasia. *N Engl J Med* 2009; 360(22): 2277-2288.

A/Prof Debbie Marriott

Candidaemia in the Australian Context: Lessons from the Australian Candidaemia Study

Introduction

Candidaemia is a recently described phenomenon with few reports of candida species bloodstream infections documented in literature prior to the mid-1950s. Since that time the rate of candidaemia has risen progressively, in part because of advances in medical and surgical management of patients. In the United States between 1980 and 1990 Candida species ranked equal 3rd with Enterococci as causative agents of nosocomial bloodstream infection and were responsible for nine per cent of cases. This compared with coagulase negative staphylococci (31 per cent) and *Staphylococcus aureus* (20 per cent).

The epidemiology of candidaemia demonstrates significant geographic variation with several studies originating outside the United States indicating stable, falling or rising incidence of candidaemia. Prior to the instigation of the Australian Candidaemia Study there was limited Australian data from a single centre which suggested that candidaemia was a significant problem and that the incidence may be rising.

It is important to understand the incidence and epidemiology of candidaemia because, put simply, of those who develop nosocomial candidaemia a third will die of candidaemia, a third will die of their underlying disease and only one third will leave hospital. It is therefore an infection of significant morbidity and mortality.

A/Professor Debbie Marriott MBBS BSc (MED) FRACP FRCPA
Senior Specialist in Clinical Microbiology and Infectious Diseases, St Vincent's Hospital

The Australian Candidaemia Study

In general the epidemiology of candidaemia has been studied retrospectively in individual institutions or prospectively in selected regions or hospitals. Therefore the data generated is not representative of all institutions serving a population. As very little information existed on candidaemia in the Australian context, the Australian Candidaemia Study was developed to describe the epidemiology, aetiology, clinical features and outcome in Australian patients who developed candidaemia. All institutions in the public and private sector covering the total Australian population of 20.1 million were invited to participate between 1 August 2001 and 31 July 2004 with the aim of collecting data and candida isolates from every case of candidaemia nationwide during the three year period. The advantage of this prospective, population-based, laboratory-directed surveillance was that it provided accurate nationwide data on the incidence, epidemiology and trends for candidaemia in the population as a whole as well as specific risk groups, thereby avoiding the distortions that occur if only selected institutions are studied.

The Australian Candidaemia Study was extremely successful, enrolling approximately 1,100 patients in 52 of the 54 public and private institutions in Australia. Only two institutions (one adult and on paediatric) refused to participate and the absence of the small number of candidaemia patients from these two institutions did not significantly alter the final results. This, therefore, is the only nationwide study completed to date in any country with extensive early and follow-up patient demographic and outcome data and blood culture isolates collected from every patient.

The amount of data obtained from the Australian Candidaemia Study was enormous and analysis continues to this day. Summaries of some of the important findings are highlighted in the following paragraphs.

Candida Species: What's in a Name?

One primary reason for the importance of local epidemiological data is the range of antifungal susceptibilities demonstrated by the different candida species. *Candida albicans* is usually susceptible to the inexpensive generic

antifungal agent fluconazole, a drug which is easy to administer both orally and intravenously and which has few side effects. *Candida glabrata* is partially or completely resistant to fluconazole in approximately 85 per cent of patients; therefore therapy requires the administration of agents that are significantly more expensive or toxic. *Candida krusei* is intrinsically fluconazole-resistant, whilst *Candida parapsilosis* is usually sensitive to the azole antifungal drugs but the echinocandin agents such as Caspofungin may have reduced activity. Within an institution these *Candida species* occur with different frequencies in different wards. For example *Candida parapsilosis* occurs with greater frequency in the paediatric setting and *Candida glabrata* is isolated more commonly in the gastrointestinal surgical and intensive care unit patients. *Candida krusei* and *Candida tropicalis* occur more frequently in haematology and oncology patients. Knowledge of the common organisms isolated within an institution and within wards or units in an institution enables a rational choice of antifungal therapy and minimises the use of expensive agents.

In the Australia Candidaemia Study *Candida albicans* was responsible for just under half (46.3 per cent) of candidaemia episodes, followed by *Candida parapsilosis* (19.9 per cent), *Candida glabrata* (15.4 per cent), with *Candida tropicalis*, *Candida krusei* and *Candida dubliniensis* accounting for 10 per cent of episodes. The remainder were caused by rare *Candida species* or polycandidal infection.

Geographic differences were seen within Australia with *Candida albicans* the predominant species in Tasmania (60 per cent), the Australian Capital Territory (77 per cent) and Western Australia (54.1 per cent). In South Australia *Candida albicans* was responsible for 37.8 per cent of episodes whereas 31.1 per cent were caused by *Candida parapsilosis*. Non-neutropenic children were more likely to be infected with *Candida parapsilosis* than other *Candida species*. In the intensive care setting, *Candida albicans* was the most common pathogen (61.7 per cent of episodes). Overall *Candida glabrata* was isolated from 18 per cent of intensive care patients but the incidence was higher in patients who had undergone upper gastrointestinal surgical procedures. The presence of *Candida glabrata* was an independent predictor of death.

Knowledge of the local patterns of *Candida species* causing blood stream infection guides clinicians in the appropriate choice of antifungal prophylaxis or treatment and is therefore an essential component of good clinical practice.

The Importance of Outpatient Candidaemia

Overall, 81.5 per cent of episodes of candidaemia were inpatient healthcare-associated whilst 11.6 per cent were outpatient healthcare-associated and 6.9 per cent were community-acquired. The finding of approximately 20 per cent of cases of candidaemia in outpatients was surprising and highlights the importance of undertaking the appropriate cultures for Candida in patients with defined risk factors. In our study, coincident malignancy, haemodialysis and diabetes were associated with outpatient healthcare-associated candidaemia whereas intravenous drug use, chronic alcohol abuse and other infectious diseases were more strongly correlated with community-acquired candidaemia. Differences in outcome were also apparent with patients developing inpatient-associated candidaemia more like to have sepsis, die within 30 days, remain in hospital longer and have concomitant healthcare-associated bacteraemia.

Quality Improvement Ancillary Measures to Improve the Outcome of Candidaemia

A number of authoritative guidelines such as those published by the Infectious Diseases Society of America and the Australian Society for Infectious Diseases suggest several quality improvement measures that should be undertaken to improve the outcome of candidaemia. These include the treatment of all patients with candidaemia, the removal of central venous catheters, follow-up blood cultures and routine ophthalmological examinations. In the Australian Candidaemia Study approximately 3/4 of patients had intravenous catheters removed within five days of candidaemia onset. Repeat blood cultures to document the clearance of candidaemia were performed in less than 2/3 patients and only 2/3 of surviving patients received at least 10 days of antifungal therapy, significantly less than the recommended 14 days. Ophthalmological examination to exclude Candida endophthalmitis is recommended routinely but was performed in less than one third of patients in the Australian Candidaemia Study. This may have a significant impact on antifungal therapy as vitrectomy with intravitreal antifungal treatment may be required to treat endophthalmitis.

These findings from the Australian Candidaemia Study indicate that significant efforts are required to improve the implementation of quality improvement guidelines and therefore to enhance patient care.

Candidaemia in Adult Cancer Patients

One hundred and third eight candidaemia episodes (33 per cent *Candida albicans*) were recognised in patients with haematological malignancy and 150 per cent (51 per cent *Candida albicans*) in solid organ malignancies in the Australian Candidaemia Study. 79 patients overall had Candida isolates with partial or complete fluconazole resistance. By multivariate analysis, prior azole therapy, gastrointestinal tract surgery in the 30 days prior to candidaemia and age greater than 65 years were predictive of fluconazole-resistant candidaemia. The 30 day crude mortality was 40 per cent in haematology patients and 45 per cent in oncology patients with fluconazole-resistant isolates associated with an increased risk of mortality. The finding that approximately 1/4 of patients

developed candidaemia with an organism with reduced fluconazole susceptibility is significant and highlights the need for this information to be integrated into surveillance and treatment algorithms.

Candidaemia Following Solid Organ Transplantation

During the period of the Australian Candidaemia Study, 24 episodes (2.2 per cent) of candidaemia were identified in solid organ transplant recipients. The overall annual estimated incidence of candidaemia in solid organ transplant recipients was three per 1000 transplant admissions, significantly higher than the incidence of 0.21 per 1000 admissions in non-solid organ transplant recipient patients. The incidence of candidaemia following solid organ transplant was influenced by the transplanted organ type with the majority of episodes in this study occurring more than six months after renal transplantation (n=14, 54 per cent). Corticosteroid therapy was a significant risk factor in this patient group. Interestingly, antifungal prophylaxis did not select for more resistant or non-*albicans Candida species* and the 30 day all cause mortality were similar to non-transplant recipients with candidaemia at 21 per cent. All deaths in this patient group occurred within five days of diagnosis, underlining a need for better diagnostic tests, targeted prevention and early treatment strategy.

Not Just Little Adults: Candidaemia in Neonatal and Paediatric Patients

In the Australian Candidaemia Study the highest rate of candidaemia occurred in neonatal patients (4.4 per 100,000 vs. 0.9 per 100,000 for children and 1.8 per 100,000 for adults). The major risk factors in neonates were prematurity and intensive care unit admission whereas haematological malignancy and neutropenia were more frequent risk factors in children. As with adults, *Candida albicans* was responsible for approximately 50 per cent of cases of candidaemia but *Candida parapsilosis* was significantly more common in neonates and children (42 per cent and 38 per cent respectively vs. 15 per cent in adults). *Candida glabrata* was uncommon in neonates and children (9 per cent and 3 per cent vs. 17 per cent in adults) and isolates from children were more likely to be fluconazole-susceptible than those from adults. Survival rates at 30 days were 78 per cent in neonates, 90 per cent in children and 70 per cent in adults. These paediatric findings from the Australian Candidaemia Study highlight the fact that age-specific differences in candidaemia occur and must be taken into consideration when developing treatment and prevention guidelines.

The Epidemiology of Candida in the Intensive Care Unit is Different From Other Areas of the Hospital

The epidemiology of Candida in the Intensive Care Unit differed from other areas of the hospital. 57 per cent of patients were male and most (67 per cent) had undergone a recent surgical procedure, 97 per cent had received recent antimicrobial therapy and 79 per cent were ventilated at the time of candidaemia diagnosis. The mean time from Intensive Care Unit admission to the development of candidaemia was eight days (range 2-86 days) and 74 per cent of episodes occurred in a tertiary referral hospital. The source of candidaemia was attributed to an intravascular device in approximately 1/3 of patients with an intra-abdominal source responsible for 10 per cent of cases.

In the intensive care setting, patients with candidaemia caused by fluconazole-resistant organisms were most likely to have had prior gastrointestinal surgery and recent prior fluconazole exposure. Knowledge of these risk factors enables appropriate choice of initial antifungal therapy.

Determinants of Mortality in Non-neutropenic ICU Patients with Candidaemia

It is well recognised that candidaemia in the intensive care setting is associated with poor clinical outcomes and excess economic costs. However the determinants of mortality – particularly those amenable to potential modifications – are not well defined. Analysis of the 183 episodes of ICU-acquired candidaemia which occurred during the Australian Candidaemia Study indicated crude hospital mortality at 30 days of 56 per cent. Host factors including older age, intensive care admission diagnosis, mechanical ventilation and failure to receive systemic antifungal therapy were significantly associated with mortality on multivariate analysis. For those patients who received initial fluconazole therapy the crude mortality was 52 per cent. However the infecting *Candida species* did not appear to be associated with mortality. The outcome was overwhelmingly related to host factors such as increasing age and haemodialysis. The high crude mortality and apparent lack of impact of treatment-related variables such as time to initiation of antifungal therapy or pharmacokinetic factors, suggest that the identification of potentially modifiable determinants of mortality is an urgent priority to attempt to reduce the mortality amongst intensive care unit patients with candidaemia.

Risk Predictive Models for Invasive Candidiasis in the Intensive Care Setting

The high cost of candidaemia in the intensive care setting, both in terms of patient morbidity and mortality and the additional cost of hospital care, suggest that improvement is needed in early diagnosis and treatment of the at-risk patients. However current clinical and laboratory approaches cannot provide early diagnostic techniques or accurately

predict those patients at high risk of infection. Therefore risk predictive models need to be developed to support clinical decisions such as the appropriate use and timing of antifungal agents. The widespread use of antifungal prophylaxis reduces the frequency of invasive candidiasis but unnecessarily exposes many patients to antifungal therapy which in turn elevates costs, selects drug-resistant isolates and increases the likelihood of adverse drug reactions and interactions. The use of empiric antifungal therapy in patients at risk of candidaemia and with clinical features of infection such as fever is also untargeted, particularly in the intensive care setting. Therefore the development of a risk prediction model which will highlight the patients at high risk of invasive candidiasis is clearly important. There have been several models in the literature but most suffer from lack of sensitivity, specificity and generalisability. For example, many risk factors of candidaemia such as gastrointestinal surgery, total parenteral nutrition, central vascular devices, prolonged mechanical ventilation and antimicrobial therapy are so common in the intensive care setting that they are of limited value in predicting individual risks.

In an attempt to derive and validate a simple, robust predictive model for invasive candidiasis that incorporated the serial assessment of patient clinical risk factors and fungal microflora, the prospective surveillance of invasive fungal infections in Australian Intensive Care Unit Study was developed. This cohort study was to be undertaken in seven Australian university teaching hospitals with mixed medical/surgical intensive care units. A generous grant from St Vincent's Clinic Foundation enabled us to participate in the initial establishment phase and to set the scene for an application for an NH&MRC grant which was subsequently awarded to the group of investigators. This has enabled the study to proceed from the initial one year to three years. Data collection will conclude within the next 12 months and it is hoped that a sensitive and specific risk prediction model will be developed from this. This in turn will support clinical decisions such as the appropriate use and timing of antifungal agents in the intensive care setting.

Conclusion

The Australian Candidaemia Study provided the first contemporary, comprehensive, population-based description of candidaemia across a continent and greatly enhanced our understanding of the epidemiology, clinical presentation and outcome of candidaemia. The importance of candidaemia in the Intensive Care Unit was highlighted and has led to the development and instigation of risk prediction studies in this setting. It is hoped that a model combining clinical risk factors with Candida colonisation will be developed which, in combination with knowledge of local fungal epidemiology, will guide early therapeutic intervention.

Dr Ian Sutton

Multiple Sclerosis and immunotherapy: The Beginning of a New Era

Multiple Sclerosis (MS) is the commonest cause of non-traumatic neurological disability in young adults and affects approximately 15,000 Australians. Multiple Sclerosis is typically a relapsing-remitting disease in which relapses become less frequent with time and 50-80 per cent of patients eventually enter a secondary progressive phase of the disease. The term "sclerosis" derives from a Greek term meaning "hardening" and the multiple areas of brain and spinal cord scarring can be readily evaluated by MRI **(see Figure 1)** which has superceded cerebrospinal fluid analysis as the diagnostic modality of choice in patients suspected of having MS.

Macroscopic pathological descriptions of patchy spinal cord and brainstem lesions were reported by Robert Carswell and Jean Cruveilhier in the 1830's and in 1868 Jean-Martin Charcot noted the presence of "grey sclerotic plaques, like scars, in the walls of the ventricles" and introduced the term "disseminated sclerosis in the form of circumscribed plaques". Charcot also identified that "disseminated sclerosis was primarily a demyelinating disorder reporting that at the microscopic level plaques were characterized by lack of myelin and specifically commented on the survival of axons.[1] While early pathological reports noted the presence of small numbers of perivascular lymphocytes these cells were considered to be a secondary reactive phenomenon. Charcot thought that the disease process arose as a result of a "suffocating of myelin" by connective tissue proliferations and trialed treatment with a number of therapies including strychnine and base metals without success.

In 1935 Rivers and Schwentker identified extensive periventricular, pontine and cerebellar demyelination in the brains of monkeys that had received repeated injections of aqueous emulsions and alcohol-ether extractions of normal rabbit brain tissue. The observation that these immunizations led to perivascular

Dr Ian Sutton MB ChB(Hons) MRCP(UK) PhD FRACP
Consultant Neurologist
St Vincent's Clinic

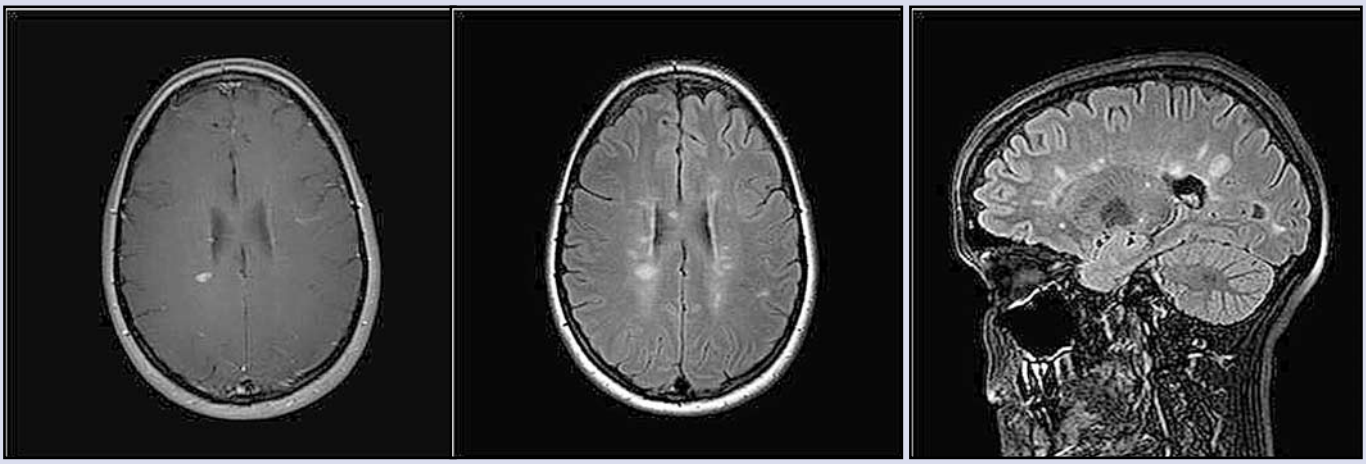


Figure 1: *Multiple Sclerosis and MRI* **A** **B** **C**

Relapsing-remitting inflammatory disease is the hallmark of MS. Serial MRI studies demonstrate the nature of the inflammatory disease. Acute inflammatory lesions are characterised by gadolinium enhancement, which can be observed on T1-weighted MRI studies. (A) Intravenously administered gadolinium is a contrast material that is normally excluded from the brain, but in the presence of inflammation there is breakdown of the blood-brain barrier (arrow). Inflammatory activity usually resolves within 4-6 weeks and lesions can either resolve completely or remain as a non-enhancing sclerotic lesion seen as a T2 hyperintense lesion on FLAIR sequence (B). Serial MRI studies show that much of the inflammatory activity in MS is sub-clinical; gadolinium enhancing lesion activity is 5-10 fold that of clinical relapse rate. (C) Sagittal FLAIR sequences show the characteristic distribution of "sclerotic plaques in the walls of the ventricles" described by Charcot. Lesions involve the corpus callosum and the ovoid peri-callosal lesions reflect peri-vascular inflammation that has occurred around venules which run perpendicular to the corpus callosum (arrowheads)

demyelination accompanied by an infiltration of mononuclear cells into the brain led to the concept of "experimental allergic encephalitis" (EAE). Continued investigation of the EAE model led to inferences that culminated in the development of an "auto-immune hypothesis of Multiple Sclerosis" in which demyelination arises as the result of myelin-specific autoimmunity that is principally mediated by auto-reactive CD4 T cells. This hypothesis is seemingly supported by multiple genetic studies which have confirmed that the gene resulting in greatest MS susceptibility is DRB1*1501 – an MHC class II allele – that presents antigen to CD4 T cells.[3]

However, it is increasingly recognized that there are significant differences between EAE and MS. Firstly there are clear differences between the pathology seen in MS and that observed in EAE. Secondly, a recent observation by Prineas and Barnett challenges the central paradigm that CD4+ T cells initiate the pathological process occurring in MS.[4] Prineas and Barnett demonstrated that the earliest pathological change observed in symptomatic MS lesions is apoptosis (programmed cell death) of oligodendrocytes (cells which form the myelin sheath) and oligodendrocyte death occurs in the absence of T cells. Thirdly, treatments that ameliorate the EAE disease process often have no effect, or on occasions can actually exacerbate inflammatory activity, in MS patients. These observations and the absence of defined antigen-specific auto-reactive processes in MS patients have caused us to revise how we conceptualise events occurring in the pathogenesis of MS. However, recent clinical trials have offered a strong body of empirical evidence confirming inflammatory processes are central to the MS disease process, at least in the early relapsing-remitting stage of the disease process.

As MS is initially a relapsing-remitting disorder, in which recovery from neurological deficits occurs as part of disease natural history, it must be emphasized that evaluation of any treatment needs to be compared to the effects of placebo. The importance of randomized controlled trials was first recognized in the 1960s when a large multi-centre study of the role of ACTH in the treatment of MS relapses led to an analysis of the outcomes of 103 ACTH-treated patients being compared to 93 placebo-treated patients.[5] While early treatment with ACTH increased the rate of recovery from relapses, use of ACTH was superceded in the 1980s by intravenous methylprednisolone which has similar effects, is easier to administer and has fewer side effects. Although steroid use shortens relapse duration consensus opinion is that regular steroid administration does not alter the long-term disease course.

The 1990s saw the emergence of interferon-β (Avonex, Betaferon and Rebif) and glatiramer acetate (Copaxone) which were the first immunomodulatory drugs to alter the natural history of MS. Pivotal clinical trials demonstrated that these therapies reduce relapse rate, MRI activity (a paraclincal measure that correlates with relapse activity) and two trials observed an accompanying reduction in disability as measured by sustained progression of expanded disability severity scale. However, many patients are either unresponsive to these drugs or demonstrated breakthrough disease highlighting the need for more effective therapies. Furthermore, side effects and injection site reactions relating to subcutaneous or intramuscular administration of these therapies have driven the demand for oral treatments or less frequent dosing schedules of intravenous therapies.

In 2007 the TGA approved the monoclonal antibody Natalizumab (Tysabri) for the treatment of relapsing-remitting MS heralding the beginning of a new era in the immunotherapeutic management of MS. Three other monoclonal antibody therapies have completed Phase II trials and two Phase III trials of oral therapies (Fingolimod and Cladribine) have recently been completed (see below) with a third oral therapy (BG-12) Phase III trial due to be completed within the next two years. Many of these therapies have mechanisms of action that specifically inhibit T cell activity thereby demonstrating a critical role of T cell-mediated inflammation in the pathogenesis of MS **(See Table 1)**.

Natalizumab is the first of the new generation of therapeutic agents to gain widespread clinical application. Natalizumab is a monoclonal antibody that binds to a4-integrins and is administered by intravenous infusion. Immune surveillance of the CNS relies on circulating T cells binding to vascular endothelial cells and this process is mediated via a4-integrin expressed on T cells binding to vascular cell adhesion molecules (VCAM) expressed on the endothelial cells. Natalizumab selectively binds to a4-integrin and inhibits T-cell trafficking into the brain and spinal cord.

The Phase III AFFIRM study demonstrated that four weekly Natalizumab infusions had a robust effect on reducing inflammatory disease activity as measured by clinical relapse rate and new gadolinium-enhancing MRI lesions compared to placebo. This dramatic effect on inflammatory activity associates with reduced disability scores compared to placebo treatment and a reduction in MRI burden of disease as measured by accumulation of T2 lesions. Furthermore, while only 7 per cent of patients receiving placebo remained free of disease activity, 37 per cent Natalizumab treated patients demonstrated no relapses, progression of disability or new MRI activity.[6]

While head-to-head comparisons of Natalizumab and interferon-β and Copaxone are lacking, most neurologists consider Natalizumab a significantly more efficacious treatment. This opinion is supported by the observation that some patients who fail to adequately respond to treatment with Interferons or Copaxone stabilise or improve after commencing Natalizumab therapy.

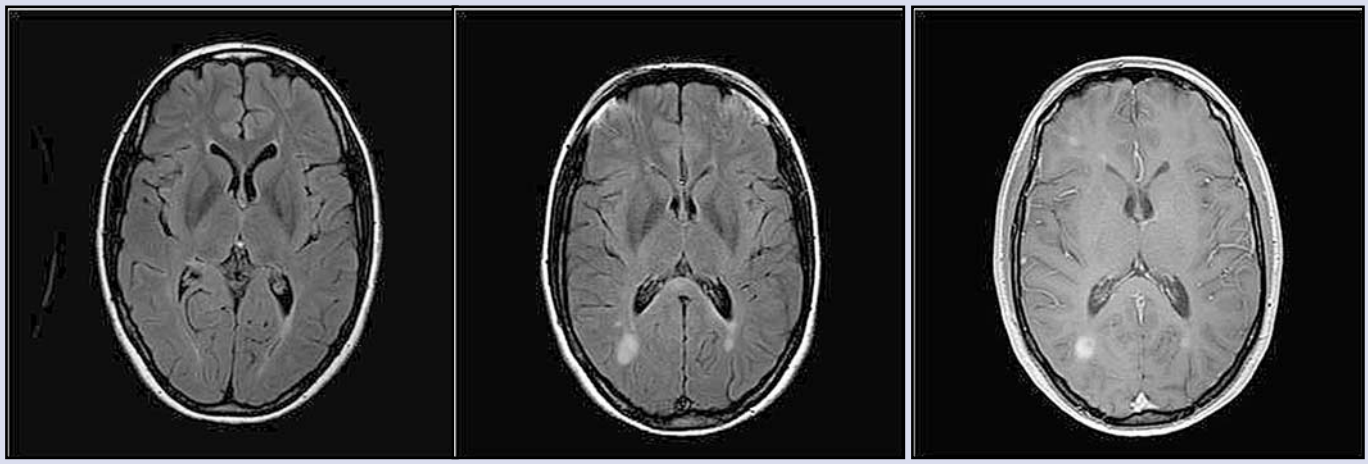
However, the prevention of T-cell trafficking into the CNS renders the brain an immune-compromised environment and Natalizumab was temporarily withdrawn one year after FDA approval following three confirmed cases of progressive multifocal leukcoencephalopathy (PML), an opportunistic cerebral infection caused by JC virus. After a careful risk-benefit analysis Natalizumab treatment was resumed and as of October 21, 2010, 70 cases of PML had been observed in 71,400 Natalizumab-treated patients. Even though the treatment effect of Natalizumab can be significantly shortened by therapeutic plasmapheresis eight cases of Natalizumab-associated PML have been fatal and many others are severely disabled. Interestingly, approximately 50 per cent of patients that have developed PML have received prior treatment with aggressive immunosuppressive therapies (such as Mitoxantrone) and the higher usage of these treatments in Europe may be relevant to the observed higher incidence of PML that is seen in Europe compared to the USA.

It is presently unclear as to whether PML is due to primary JC virus infection, or reactivation of latent JC virus infection in the brain or bone marrow of infected patients. Furthermore routine clinical monitoring for early diagnosis of PML can be confounded by MRI changes of PML being difficult to distinguish from those changes arising as a result of the underlying MS disease process and failure to detect JC virus in the CSF of infected patients even with extremely sensitive polymerase chain reaction (PCR) assays. A recent report of an assay that looks at individual exposure to JC virus and rates of sero-conversion suggests that 40-50 per cent of the population are sero-negative with a sero-conversion rate of 1-2 per cent per year. In JC virus sero-negative Natalizumab treated patients the risk of PML is estimated at 1:33,000.[7]

In addition, to Natalizumab there are three other monoclonal antibodies (Alemtuzumab, Daclizumab and Rituximab) that show promise in the treatment of MS. Alemtuzumab (Campath-1 H) targets CD52 and induces profound and long-lasting lymphopenia, with CD4 cells taking up to five years to reach pre-treatment levels allowing the drug to be administered annually. The CAMMS-223 Phase II study demonstrated Alemtuzumab had greater efficacy than interferon-1a (Rebif) in reducing relapse rate and while patients taking Rebif demonstrated progression of disability the average EDSS of Alemtuzumab-treated patients improved.[8]

The advent of Alemtuzumab and Natalizumab use has led to the emergence and recognition of immune reconstitution syndromes occurring in MS patients for the first time. Alemtuzumab induces a profound depletion of CD4 T cells and as the lymphocyte populations start to recover 20-30 per cent of patients develop autoimmune thyroid disease and less frequently other autoimmune conditions such as idiopathic thrombocytopenic purpura (ITP), Goodpasture's and primary ovarian failure. The effects of immune reconstitution have also been observed in patients treated with Natalizumab, most notably in the small sub-group of patients that develop PML due to JC virus, where immune reconstitution (which may be more rapidly induced by plasmapheresis to remove circulating Natalizumab) correlates with a clinical deterioration. In addition, in patients that electively cease Natalizumab therapy recurrence of MS disease activity occurs three to four months after the last infusion and in patients with high levels of pre-therapy activity this effect of recurrent disease can be more pronounced than that seen prior to commencement of treatment **(Figure 2)**.

Two oral therapies (Fingolimod and Cladribine) are expected to be available for use in relapsing-remitting MS within the next year or two. Cladribine is metabolized to 2-chlorodeoxyadenosine triphosphate which inhibits DNA synthesis resulting in selective T cell depletion and in a two year trial the risk of relapse in Cladrabine-treated patients was half that seen in the placebo arm.[9] While the TGA have approved Cladribine use in Australia for a maximum treatment period of two years, the European Medicines Agency Medical Advisory Board has currently recommended against approval of Cladribine treatment as there are



A B C

Figure 2: *CNS Immune reconstitution and recurrent inflammation with cessation of Natalizumab treatment*

A 36-year-old female with 9 relapses in 3 years and 8 months prior to commencing Natalizumab treatment experienced no relapses while receiving 12 Natalizumab infusions between June 2008 and April 2009. In early August 2009 the patient described recurrence of spinal cord symptoms and "feeling in a fog". A progress MRI brain demonstrated at least 15 acute gadolinium-enhancing lesions. (A) An axial FLAIR section 7 weeks prior to stopping therapy shows no lesions. (B) New lesions were observed on progress imaging in August 2009. (C) All new lesions show gadolinium-enhancement consistent with recrudescence of acute inflammatory activity due to immune reconstitution of the CNS.

Table 1: *Many of the emerging therapies in MS selectively target T cell immune responses*

Drug	Formulation	Target	Mechanism of action	Current Status
Natalizumab (Tysabri)	Monoclonal antibody	a4-integrin	Inhibits T cell trafficking into CNS	>71,000 treated patients
Alemtuzumab (Campath-1 H)	Monoclonal antibody	CD52	Profound and prolonged lymphopenia (mainly CD4 T cells)	Phase III trial
Fingolimod (Gilenia)	Tablet	Sphingosine 1-Phosphate	Central memory T cell retention within lymph nodes	FDA approved
Cladribine (Movectro)	Tablet	T cell DNA synthesis	T cell lymphopenia	TGA approved for maximum of 2 years

concerns regarding Zoster infection and long-term malignancy risk. Fingolimod is a fungal derivative that is a partial agonist of Sphingosine 1-Phosphate that prevents egress of central memory T cells from lymph nodes. Fingolimod has proven to be more efficacious than both placebo[10] and interferon-1a (Avonex)[11] in head-to-head trials. While the safety data for Fingolimod are encouraging to date there remain concerns regarding the long-tem safety in patients that are chronically immunosuppressed.

It is apparent that the next decade will offer a range of increasingly effective treatment options for patients with relapsing-remitting MS, however all emerging therapies carry small but substantial risks. This presents a new challenge in assessing the potential benefits against the risks of treatment. It is often difficult, and in most cases impossible, to determine prognosis at the onset of the disease process. While these new treatment options are a welcome addition to our somewhat deficient therapeutic armamentarium there remain many unanswered questions as to how best individualise therapy in a disease that has such a broad range of potential outcomes.

References:

1. **Charcot JM.** "Histologie de la sclerose en plaques" *Gazette des Hospitaux*, Paris 1868;41:554-555
2. **Rivers TM, Schwenkter FF.** Encephalomyelitis accompanied by myelin destruction experimentally produced in monkeys. *J Exp Med* 1935;61:689-702
3. **The International Multiple Sclerosis Genetics Consortium.** Risk Alleles for Multiple Sclerosis Identified by a Genomewide Study. *N Engl J Med* 2007;357:851-62
4. **Barnett MH, Prineas JW.** Relapsing-remitting multiple sclerosis: pathology of the newly forming lesion. *Ann Neurol* 2004;55:458-68
5. **Rose AS, et al.** Cooperative study in the evolution of therapy in multiple sclerosis: ACTH versus placebo final report. *Neurology* 1970:20;1-59
6. **Polman CH, et al.** A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354:899-910
7. **Gorelik L, et al.** Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurol*. 2010;68:295-303
8. **CAMS223 Investigators.** Alemtuzumab vs. Interferon-beta 1a in early multiple sclerosis. *N Engl J Med* 2008;359:1786-801
9. **Giovanoni G et al.** A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010;362:416-426
10. **Kappos L. et al.** A placebo-controlled trial of oral fingolimod in multiple sclerosis. *N Engl J Med* 2010;362:387-401
11. **Cohen JA, et al.** Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010;362:402-415

The Sandra David Oration

In Life and Death: How do we honour the Patient's Autonomy and the Doctor's Conscience?

Fr Frank Brennan SJ AO*

Christian healers know well this story of Jesus:

On the sabbath Jesus went into the synagogue and taught, and there was a man there whose right hand was withered. The scribes and the Pharisees watched him closely to see if he would cure on the sabbath so that they might discover a reason to accuse him. But he realized their intentions and said to the man with the withered hand, "Come up and stand before us." And he rose and stood there. Then Jesus said to them, "I ask you, is it lawful to do good on the sabbath rather than to do evil, to save life rather than to destroy it?" Looking around at them all, he then said to him, "Stretch out your hand." He did so and his hand was restored. But they became enraged and discussed together what they might do to Jesus. (Lk 6:6-11)

I thought Jesus had it easy on one count. The autonomous man with the withered hand wanted Jesus the conscientious healer to do good rather than evil, to save life rather than destroy it. The legalism of the religious authorities could be readily disregarded because the patient's autonomy and the healer's conscience could be honoured by the performance of an agreed healing. But what of the case when the autonomous patient wants the conscientious doctor to perform an action which the doctor thinks wrong and death dealing? And what of the case when the autonomous patient wants the conscientious doctor to desist from doing what the doctor thinks is good and life giving?

The consideration of medico-legal problems in the public square of a pluralistic democratic society keeping pace with profound technological change is often marked by simplistic assertions, precluding considerations of comprehensive world views, whether religious or philosophical. It is now commonplace for doctors to be told to leave their consciences at the door, as their patients are consumers and they are suppliers and of course the market decides. It is suggested that the doctor has a stark choice: "What's to come first, the patient or the ethics?" Debates about law and policy are often resolved with simplistic assertions about individual rights and autonomy, with little consideration for the public interest, the common good, and the doctor-patient

relationship. Even conscience is said to be a matter for contracting out.

When considering questions such as: "Should euthanasia be legalized?", I seek to distinguish between questions of law, public policy and morality. Many persons of a religious persuasion may reason morally from presumptions such that life is a gift given by God and that it is not for any person including the suffering self to take away that life. Such presumptions cannot ground public policy and law, at least in a society where those presumptions do not enjoy uncontroversial, broad public support.

Those who support the legalization of euthanasia usually proceed by quoting cases of mentally competent patients who are not depressed but who are suffering unbearable pain, facing terminal illness. The easiest and most compelling case to consider is the patient whose relatives fully support the proposed euthanasia. There is no suggestion that the relatives are exerting undue influence on the patient for their own self-interested reasons. There are good palliative care facilities available so it is not as if the patient is under duress, feeling that she has no option but death. The patient has a good and trusting relationship with her medical team. Under existing law and policy, there is already the possibility that such a patient will be euthanized or at least given increased doses of pain which will hasten death. A 1997 study on "End of life decisions in Australian medical practice" published in the Medical Journal of Australia by Peter Baume and Peter Singer et al claimed that "while 30% of all Australian deaths were preceded by an action or omission explicitly intended to end the patient's life, in only four was the decision taken in response to an explicit request from the patient."

Given that some medical practitioners presently practise euthanasia when the law prohibits same, is there any point in changing the law? The usual reasons for legal change include the claims that some jurisdictions have been able to develop sufficient safeguards to ensure that only the competent, self-determining patient can avail the service of physician assisted suicide and that without such a change to the law, competent, self-determining citizens have to opt for earlier suicide when they are still able to self-administer the suicide cocktail.

If there is to be any move towards the legalization of euthanasia, there will be considerable difficulty in setting criteria and safeguards. It is all very well restricting its availability to the competent, but what of the claim of the person who says, "I am now competent but I am not yet ready to die. Soon I will be incompetent and I want to have made a binding decision consenting to euthanasia once I have lost my competence. I do not want to go earlier than I need. But I do want to go once I am no longer competent." Inevitably there will be some individuals who in the transition to incompetence or dementia will have changed their flickering minds and decided to cling to life for all that it is worth. At their moment of greatest vulnerability, the law will be invoked with a presumption that their earlier option for death is now binding and unreviewable.

I acknowledge that many ageing persons could autonomously decide to end their own lives according to their own sense of a good life and a good death, whatever the law was. But what of vulnerable groups such as Aborigines in the Northern Territory who were not adequately consulted and who were terrified by the 1997 Northern Territory euthanasia law? Many of them were suspicious of, or alienated from, the healthcare system, having been told that non-Aboriginal doctors would be able to kill them in certain circumstances without fear of prosecution.

There are many other individuals who might be vulnerable though they do not fit any minority group profile – those like the late Alzheimer's sufferer Graeme Wylie and his daughters. When sentencing Shirley Justins for providing Wylie with a lethal dose of the veterinary drug Nembutal, the judge observed that it was cruel for those involved in the euthanasia to deny Mr Wylie's daughters an opportunity to say farewell. Given Dr Philip Nitschke's involvement in that case, there would be every chance of there being more Graeme Wylies who would never come to our attention once euthanasia was legalised and doctors like Nitschke were free to practise euthanasia more than they presently do.

Many voluntary euthanasia supporters may enjoy a good death regardless of the law. There are some "oldies" who will be vulnerable if euthanasia is legalised. Not all oldies are vulnerable; but some are. In shaping laws and policies (rather than moral codes), we need to have a care for them, regardless of our religious or atheistic beliefs.

Earlier this year, voluntary euthanasia advocates joined issue with my description of Graeme Wylie's death. Not having attended the trial of Shirley Justins, I have confined myself to facts on the public record. There was a family dispute about the belated changes made to his will – a not unfamiliar occurrence in Australia. Wylie had previously sought the services of Dignitas in Switzerland but been rejected because he was judged not competent. But letter writers to the *Sydney Morning Herald* (which has a strong pro-euthanasia editorial policy) have seen no problem with this. One letter writer (Dorothy Kamaker, *SMH Letters*, 10 February 2009) thought he was competent to give orders for his own death. Another (Alan Mann, *SMH Letters*, 10 February 2009) thought Wylie would be eligible for euthanasia under euthanasia legislation with stringent verification procedures.

Wylie's daughters were denied a chance to farewell him. When Justins was sentenced, Wylie's daughter, Tania Shakespeare, told the media, "I'm heartbroken that I wasn't able to say goodbye to my father". The sentencing judge said Justins was selfish and cruel for denying the daughters an opportunity to say farewell. Kep Enderby who attended Justins' trial disputed the judge's assessment (*SMH Letters*, 11 February 2009).

The complex Wylie case highlights how fraught any euthanasia law would be, regardless of the stringent verification procedures involved. Regardless of our religious affiliations or comprehensive world views, we should exercise great prudence before approving any law which departs from the principle

"do no harm", regardless of the utility such change would offer the competent.

In 2008, Victorians confronted a novel problem with the invocation of the "do no harm" principle and freedom of conscience at the other end of the life cycle. The comprehensive abortion law reform legislation designed to guarantee legal abortion post-viability as well as pre-viability included a provision requiring a medical practitioner with a conscientious objection to providing an abortion in the particular instance to refer the patient to another practitioner known not to have the same objection. The provision is not only unprincipled; it is unworkable. Since then, the Australian Medical Council has been consulting on a national code of ethics for all Australian doctors. During their consultation, they reported that "there was a request for clear guidance in relation to conscientious objection". The new code provides guidance, in contradistinction to the Victorian law. The Code states:

Good medical practice involves:

Being aware of your right to not provide or ***directly*** *participate in treatments to which you conscientiously object, informing your patients and, if relevant, colleagues, of your objection, and not using your objection to impede access to treatments that are legal.*

Not allowing your moral or religious views to deny patients access to medical care, recognising that you are free to decline to personally provide or participate in that care.

Some might prefer that the word "directly" be omitted. But it is quite arguable that legally enforced direct referral for a procedure that does not usually require a referral and which otherwise would not be performed except after appropriate counselling would constitute "direct participation". A conscientious objector would be entitled not to formally refer in these circumstances. The Victorian Medical Practitioners' Board has power to discipline or even strike off practitioners for non-compliance with Victorian law. Before such action was taken by the Board, it, being a public authority for the purposes of the Victorian *Charter of Human Rights and Responsibilities Act*, would need to ensure that it did not act in a way that is incompatible with the human right of freedom of conscience. The new Code should be a sure guide for the Board.

Given that the referral clause was both unnecessary, unworkable, and more intrusive than state notification of available abortion providers, one can only conclude as did Justice Kennedy in the leading US gay rights decision *Romer v Evans*: the clause "seems inexplicable by anything but animus toward the class it affects; it lacks a rational relationship to legitimate state interests."

In August 2009, Chief Justice Martin gave a very sensible, uncontroversial decision in the Western Australian Supreme Court in the case *Bridgewater Care (Inc) and Rossiter*. Mr Christian Rossiter is a profoundly disabled quadriplegic who is presently receiving nutrition and hydration through a PEG. He has had enough of life and wants his carers at Bridgewater Care to discontinue feeding him. The "right to life" and "right to die" advocates have been having a field day. You would think they had not read the judgment.

The Chief Justice said:

It is important I think to emphasise at the outset what this case is not about. It is not about euthanasia. Nor is it about physicians providing lethal treatments to patients who wish to die. Nor is it about the right to life or even the right to death. Nor is the court asked to determine which course of action is in the best interests of a medical patient. The only issue which arises for determination in this case concerns the legal obligations under Western Australian law of a medical service provider which has assumed responsibility for the care of a mentally-competent patient when that patient clearly and unequivocally stipulates that he does not wish to continue to receive medical services which, if discontinued, will inevitably lead to his death.

The judge said that if Mr Rossiter, having received competent medical advice, decided to request Bridgewater to cease administering nutrition and hydration, then in the absence of any revocation of that direction by Rossiter, Bridgewater should cease to provide nutrition and hydration. There would be no risk of criminal liability. The only risk would arise if the caregiver were to continue feeding without consent and direction because that could be an assault or a trespass on the person of Mr Rossiter.

This was nothing like the case of a person in a persistent vegetative state without the competence to decide and unable to communicate with the caregiver. As the judge made plain: "Mr Rossiter is not a child, nor is he terminally ill, nor dying. He is not in a vegetative state, nor does he lack the capacity to communicate his wishes. There is therefore no question of other persons making decisions on his behalf. Rather, this is a case in which a person with full mental capacity and the ability to communicate his wishes has indicated that he wishes to direct those who have assumed responsibility for his care to discontinue the provision of treatment which maintains his existence."

The reactions of the "Right to Life" and the "Right to Die" advocates were equally misleading and unhelpful. It is not only illegal, it is also immoral for a person to trespass on the body of a competent person, especially when consent has been sought and withheld. It is not only against the law. It is wrong. It is morally objectionable. Churches with a strong teaching tradition should assist their members to form and inform their consciences that they should not trespass on the bodies of the mentally competent without consent.

In future, the tasks of our parliaments and our courts will be more difficult if the reasoned voice of experience is not heard from churches who know what they are talking about when it comes to health care. Unless we are at the bedside in constant dialogue with the clinicians, we too risk becoming ideologues.

Bishop Anthony Fisher OP has now said, 'No one should force feed (Mr Rossiter) and if he is saying "No" to tube feeding, his nursing home is probably right to follow his instructions. As I understand, the bishop's concern was

whether Rossiter was mentally competent to make such a request, in particular, whether he may have had undiagnosed and untreated depression. In this case, given the clarity that has been brought to the matter in the court proceedings, including the judge's finding that Rossiter was mentally competent and there being so suggestion of depression, I would go one step further and say that the nursing home would undoubtedly be wrong not to follow his instructions. After all, "treatment should not be administered to any competent patient…until the patient's free and adequately informed consent has been given". I would invoke the Code of Ethical Standards for Catholic Health and Aged Care Services in Australia at #1.16:

Patients have the moral right to refuse any treatment which they judge to be futile, overly burdensome or morally unacceptable, and such refusals must be respected. In addition, healthcare practitioners may not override any refusal of treatment by a competent patient who is not mentally disturbed, clinically depressed or suicidal, irrespective of whether or not they agree with the patient's refusal.

I would see no application in a case like *Rossiter* for the rider: "There is, however, an obligation to prevent suicide when this is possible." Though some persons, including many Catholic health providers, might agree with Pope John Paul II that the "administration of water and food, even when provided by artificial means, always represents a natural means of preserving life, not a medical act", others (including Mr Rossiter) are entitled to take a contrary view. Even if the competent patient be wrong in his bioethical classifications, he is still entitled to insist that those with the viewpoint of Pope John Paul II desist from interfering with his bodily integrity by administering what he regards as an unwelcome medical act, a treatment that he regards as morally unacceptable, overly burdensome or futile. Even if there be a case for disputing Mr Rossiter's ethical analysis, there is no case for interfering with his bodily integrity against his wishes.

Furthermore, Christian charity may point to supporting him as he confronts death. Christian morality does not necessarily dictate that the health care provider of good conscience terminate any relationship with him. Could not a Catholic facility in good conscience continue to provide care and spiritual support for such a competent patient while honouring his wishes? I am not saying that a Catholic facility would be obliged to, but neither do I think that a Catholic facility would be obliged to show him the door or force feed him as he approaches death. There is nothing new in this. My own mother was a young doctor at the Brisbane Mater Public Hospital in 1951 when the patient in the bed at the end of the ward was a Jehovah's witness who received nothing but food, water and good pastoral care because he refused a necessary blood transfusion. He was not forcibly treated nor shown the door.

Neither the law nor directives from religious authorities will resolve all these future cases. The delivery of optimum health care will always require the application of the health professional's formed and informed conscience. The health professional will always have to consider additional ethical questions when treating the incompetent patient. In a Catholic health care facility, the conscientious decisions of health care professionals will need to be augmented by Christian charity extended even to the autonomous patient whose ethical judgments we do not share. With sound formation and leadership by our religious authorities we might even be able to assist others who do not share our faith tradition in the making of ethical decisions.

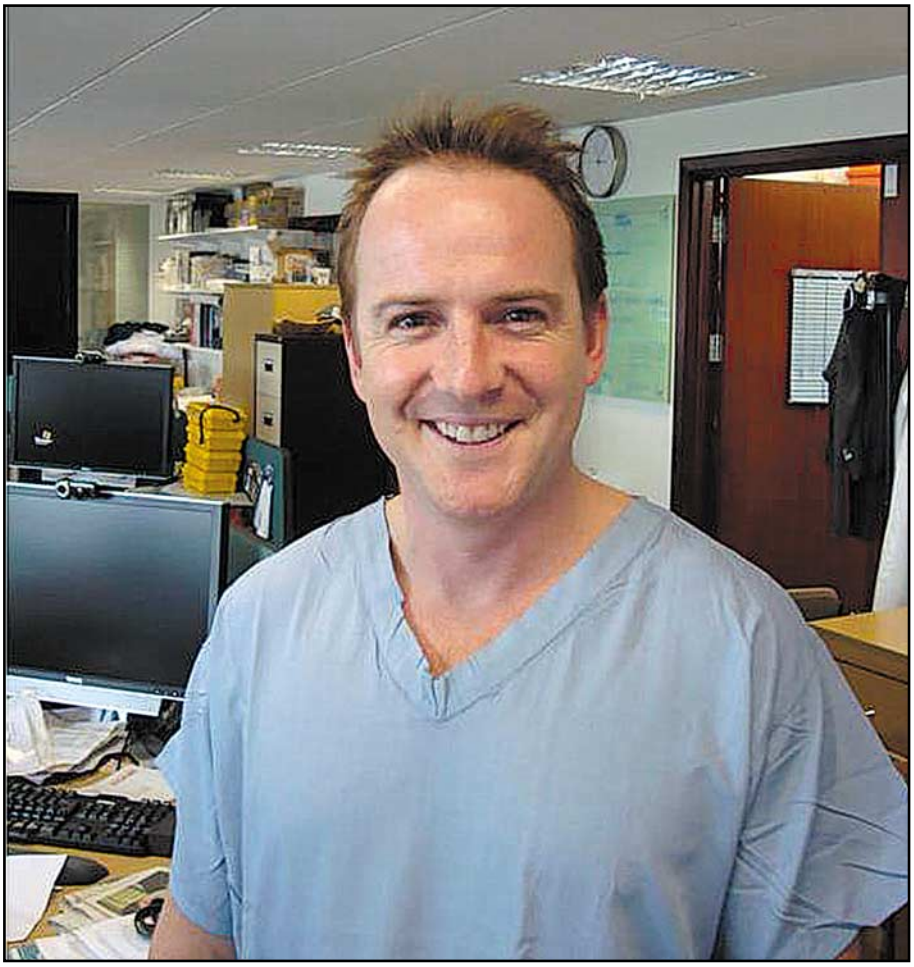
References

1. Helga Kiuse, Peter Singer, Peter Baume, Malcolm Clark and Maurice Rickard, "End of life decisions in Australian medical practice", 1997 Medical Journal of Australia
2. *Romer v Evans* 517 US 620 (1996) at 633
3. [2009] WASC 229
4. Catholic Weekly, 23 August 2009
5. Catholic Health Australia, Code of Ethical Standards for Catholic Health and Aged Care Services in Australia, Catholic Health Australia, 2001, p. 13, #1.5
6. Ibid, p. 16
7. Ibid.
8. John Paul II, Address to the International Congress on 'Life Sustaining Treatments and Vegetative State', 20 March 2004, p. 2

*Frank Brennan SJ AO is a professor of law in the Institute of Legal Studies at the Australian Catholic University, Chair of the National Human Rights Consultation Committee and National Board Member, St Vincents Health Australia

Dr David Roy

Perioperative Management of Patients with Coronary Stents during Non-Cardiac Surgery



David Roy
MBBS, MRCP, FRACP.
Interventional Fellow, Cardiology Department, St Vincent's Hospital

David Baron
FRACP., FCCP, FACC, FCSANZ
Senior Staff Specialist, Cardiology Department, St Vincent's Hospital
Consultant Cardiologist, St Vincent's Private Hospital and St Vincent's Clinic

David Muller
MD, FRAC., FACC, FCSANZ
Director, Cardiac Catheterization Laboratories, St Vincent's Hospital
Consultant Cardiologist, St Vincent's Private Hospital and St Vincent's Clinic

Paul Roy
FRACP, FRCP, FACC, FCSANZ
Interventional Cardiologist, St Vincent's Hospital
Consultant Cardiologist, St Vincent's Private Hospital, St Vincent's Hospital and St Vincent's Clinic

Stenting And Anti-Platelet Therapy

Increasing longevity and the increasing use of coronary stents has meant that many non-cardiac surgeons are presented with the dilemma of what to do with the stented patient's antiplatelet regime in the peri-operative period. Coronary stent implantation requires that the antiplatelet drugs, Aspirin and Clopidogrel are given for one year and thereafter Aspirin alone is given indefinitely. Aspirin is usually given in a dose of 300mgs daily for the first three months and 100mgs thereafter. Clopidogrel is given in a dose of 75mgs daily.

Activated platelets promote vascular wall inflammation and lead to the subsequent generation of thrombin and platelet-platelet aggregates, which mechanically obstruct antegrade coronary blood flow.[1]

Aspirin appears in the blood within 10 minutes after absorption and achieves a peak plasma concentration within 30-40 minutes. Aspirin is rapidly metabolised by blood esterases and the liver. The major metabolite, salicylate, has a half-life of three to six hours and can be detected in both plasma and urine. The target for Aspirin is cyclo-oxygenase (COX). In platelets, COX is largely responsible for generation of thomboxane A_2 (TXA_2), which is a potent vasoconstrictor and platelet agonist. Aspirin is a non-selective

irreversible inhibitor of COX enzymes and as a result thromboxane production is blunted for the lifetime of the platelet (approximately ten days). New platelets must be generated de novo to re-establish COX activity.[1] This is clinically relevant because Aspirin is characterised by a long-lasting antiplatelet effect despite its rapid metabolism.

There are many platelet aggregation tests (eg. thromboxane levels, platelet aggregation with ADP, platelet aggregation with collagen etc), but unfortunately no currently available test will determine the level of Aspirin effect. Platelet aggregation tests done currently will simply tell you that there is an Aspirin effect but not quantitate this effect.

Platelet inhibition with both Aspirin and Clopidogrel has a major role both in the treatment of acute coronary syndromes[9] and particularly for the prevention of ischaemic complications of coronary stenting.[2,3]

There have been several studies undertaken which have shown great variability in responsiveness to Aspirin with some patients being non-responders.[4,5] These patients have a greater incidence of cardiovascular events despite being on Aspirin. Alternatively there may also be hyper-responders.

Clopidogrel bisulphate, a thienopyridine is rapidly absorbed in the intestine. It is converted into its active thiol metabolite by hepatic cytochrome P450 enzymes and achieves a peak plasma level approximately one hour after dosing. It binds to the platelet P2Y12 receptor which results in selective and irreversible inhibition of the binding of ADP to the platelet P2Y12 receptor.

There are multiple reasons for Clopidogrel non-responsiveness including alterations in the activity of cytochrome P450 caused by drug interactions between Clopidogrel and lipophilic statins,[6] calcium channel blockers and perhaps Omeprazole.

Genetic polymorphism of cytochrome P450 may also be a cause for variable platelet reactivity to Clopidogrel.

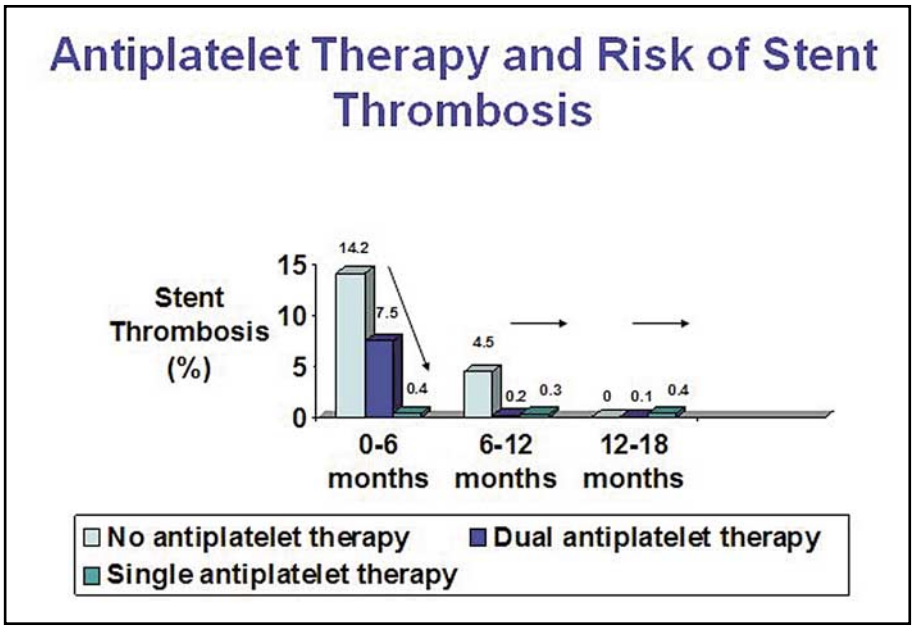


Figure 1: *Antiplatelet Therapy and Risk of Stent Thrombosis.*

As with Aspirin, laboratory studies of the effect Clopidogrel on platelet aggregation are not quantitative and as yet not freely available.

Laboratory testing of overall platelet function is limited by several factors. Firstly, they are performed on citrate-anticoagulated blood. Secondly, blood is often stored for a variable period of time before testing, and thirdly, the assessment of thrombotic status on the basis of platelets response to only one or two agonists ignores the complexity of the mechanism of platelet thrombus formation in vivo.

The majority of coronary stents currently used are drug eluting (DES) stents. These stents are coated with a drug (sirolimus or a derivative) which delays endothelialization of the stent and prevents the overgrowth of neointimal tissue which can lead to stent restenosis. There are known benefits of these stents compared to bare metal stents (BMS) in terms of their efficacy in reducing clinical and angiographic restenosis.[2,3]

In a group of patients who received a DES early discontinuation of Clopidogrel was the most important risk factor for stent thrombosis.[7]

Stent thrombosis can occur acutely (within 24 hours), subacutely (within 30 days) or as late as one year (late) or more (very late) after stent placement. Stent thrombosis in the first year appears to occur with equal frequency in patients with BMS or DES, as long as patients with DES are treated with dual antiplatelet therapy (Aspirin plus Clopidogrel).

The period of risk requiring dual antiplatelet therapy is longer with DES due at least in part to delayed neointimal coverage. The risk for very late stent thrombosis is slightly higher with DES than BMS and it is unknown whether longer term dual antiplatelet therapy reduces this risk **(Figure 1)**.

Most cases of stent thrombosis occur within the first thirty days after placement, irrespective of stent type. The best available data in the real world population comes from the Dutch stent thrombosis registry in which 437 of 21,009 (2.1 per cent) patients had definite stent thrombosis during a median follow up of 31 months.[8] Stent thrombosis was acute in 32 per cent, subacute in 41 per cent, late in 13 per cent and very late in 14 per cent. Whereas restenosis is a relatively benign event, stent thrombosis is associated with a high risk of death or a large myocardial infarction.[8]

BMS thrombosis is usually acute (first 48 hours). Late and very late BMS thrombosis is uncommon.

In the Sirius trial of 1,058 patients, at five years, there was no significant difference in the rates of stent thrombosis in the DES and BMS groups (1.2 per cent versus 1.8 per cent), but BMS thrombosis occurred early.[9]

Early Non-Cardiac Surgery

Studies in patients receiving BMS have shown that major non-cardiac surgery within the first six weeks and particularly within two weeks of stent implantation (associated with cessation of antiplatelet drugs) carries an appreciable risk of stent thrombosis. Limited data suggests a similar risk for DES that extends for a longer duration.[10]

To try and reduce the risk of stent thrombosis several factors need to be considered at the time of stent placement:

- Angiographic features
- Risk of future bleeding
- Drug compliance
- Short-term need for non-cardiac surgery

For example, if a patient needing a coronary stent was known to require hip or knee surgery in the next few months it may be prudent to use a bare metal stent where cessation of Clopidogrel at three months may not pose as high a risk in the BMS compared to the DES. Ideally of course Aspirin should be continued during the perioperative period. Likewise if a patient requiring a coronary stent is known to be unreliable and likely to be non compliant, a bare metal stent may also be safer in the long term.

If, after stenting, previously unplanned non-cardiac surgery becomes essential consider:

- What is the risk of stent thrombosis?
- What is the risk of bleeding?
- What is the consequence of bleeding?

The Cardiac Society of Australia and New Zealand has guidelines for antiplatelet therapy in patients with coronary stents undergoing non-cardiac surgery. These guidelines are very similar to those proposed previously by the American College of Cardiology and the American Heart Association. Many associated societies have contributed to the Australian guidelines (Royal Australian College of Surgeons, the Orthopaedic Society, etc.). The risk of stent thrombosis can be evaluated as per the diagram **(Figure 2)**.

Currently, the Cardiac Society of Australia and New Zealand recommends: elective non-cardiac surgery should be deferred for at least six weeks and ideally three months following BMS (Level of Evidence 3, Grade of Recommendation A); and

Elective surgery should be deferred for twelve months following DES (Level of Evidence 3, Grade of Recommendation B).

The evaluation of risk for stent thrombosis can be considered by following the flow chart outlined in **Figure 3**. Detailed consideration of all these factors may require a call to the cardiologist involved in the patient's management and this is advisable for any patient having non-cardiac surgery in the first twelve months.

As well as assessing the thrombotic risk of ceasing antiplatelet agents, it is also important to assess the haemorrhagic risk of the planned surgery should antiplatelet agents particularly Aspirin alone be continued. The doctor should consider the urgency of planned surgery and whether it can be delayed. If not, the consequences of bleeding for that operation should be assessed. Certain operations such as intracranial, spinal, extraocular, plastic reconstructive and non-laser T.U.R.P., have an unacceptable risk of bleeding. With these exceptions, wherever possible, continuation of antiplatelet therapy is recommended in patients with prior coronary artery stenting undergoing non-cardiac surgery.

If the perioperative antiplatelet therapy needs to be ceased because of the high risk of bleeding then it may be necessary to consider some bridging treatment. Though Heparin or low molecular weight Heparin are often considered in this context they are not strong antiplatelet agents and there is no current evidence that they make any difference. Generally Heparin is used but, as mentioned above, there is no evidence for its efficacy in this situation. Theoretically the only measure that could be used intravenously on a short term basis, is to use a drug such as Tirofiban which completely blocks the effect of platelets over a 24 hour period but does carry its own bleeding risks during and after surgery.

The most important factor in these situations is that the patient should have their non-cardiac surgery in an Institution where direct access to a cardiac catheter laboratory and an interventional facility is available should stent thrombosis occur. Should the patient be unfortunate enough to have an acute thrombosis the affected vessel could be rapidly reopened in the appropriate setting of a hospital with interventional facilities.

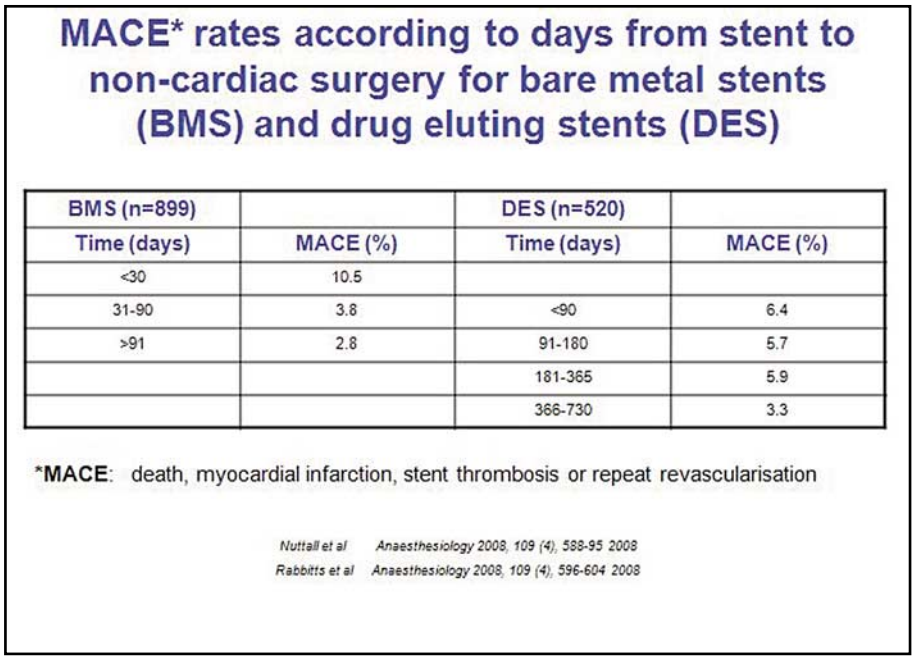


Figure 2: *MACE (major adverse cardiovascular event) rates are higher for DES than BMS when antiplatelet drugs are ceased.*

Summary

Surgeons should take particular care in operating on patients with previous coronary stents.

Consultation with the patient's cardiologist is advisable. Non-cardiac surgery in a patient with a coronary stent should be undertaken in a facility where

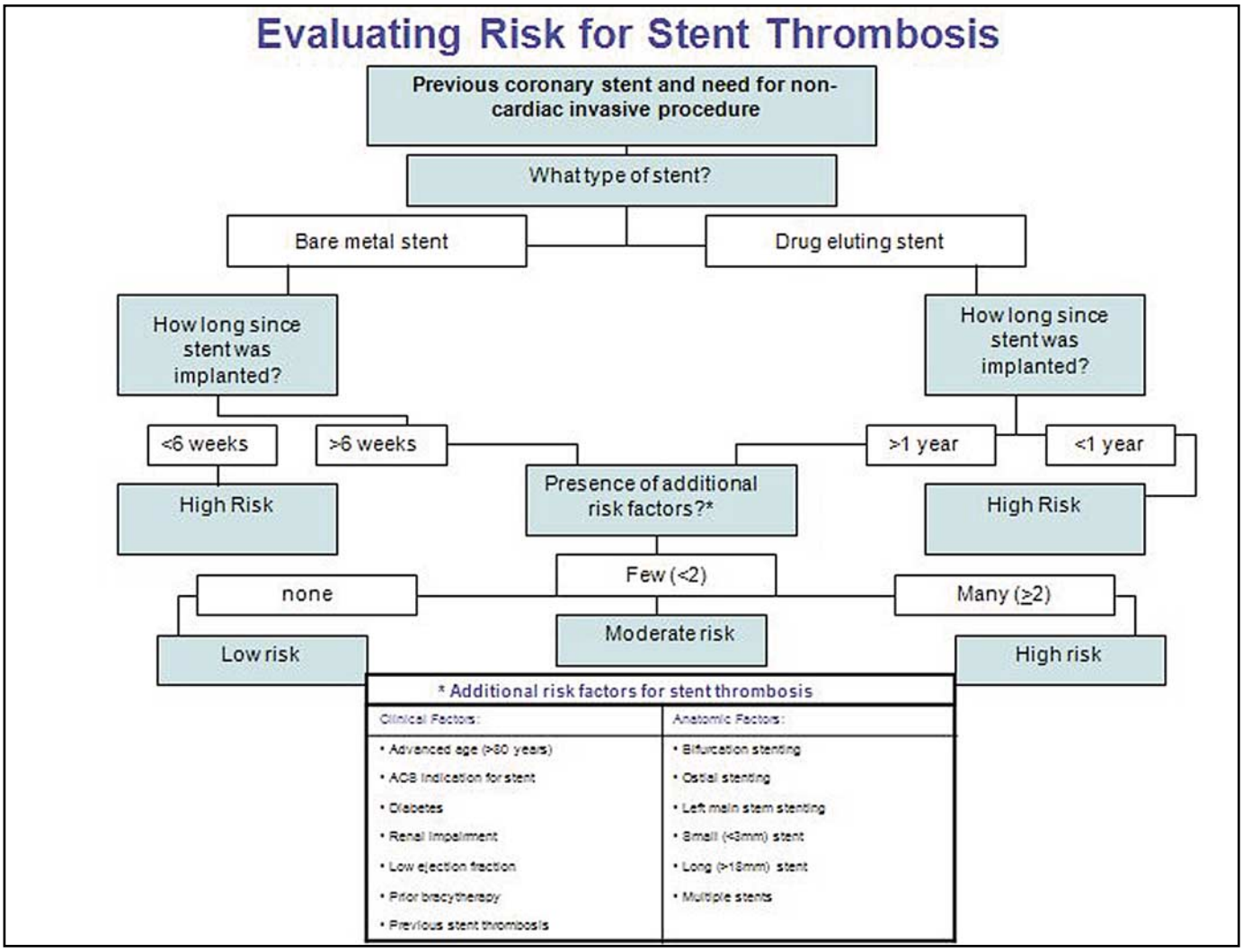


Figure 3: *Evaluation of the risk for Stent Thrombosis.*

cardiac intervention is available 24 hours a day and the patient should be monitored in a high dependency area in the perioperative period.

Death, myocardial infarction, stent thrombosis and the need for urgent cardiac revascularization are increased if non-cardiac surgery is performed within six weeks of bare metal stenting (5-30 per cent). There would appear to be further reduction of risk if surgery is deferred for at least three months following implantation of a bare metal stent.

Perioperative death, myocardial infarction and stent thrombosis occurs in at least 5 per cent of patients if dual antiplatelet therapy is ceased and non cardiac surgery is performed within twelve months of drug eluting stent placement.

Despite the observation that dual antiplatelet therapy increases the likelihood of bleeding from most surgical procedures, the consequences of this bleeding are generally less significant than those of stent thrombosis if certain types of surgery (eg intracranial) are excluded.

Currently, there is evidence that second generation drug eluting stents have a lower risk of stent thrombosis than previously documented for first generation stents.[11] Biodegradable stents are being developed and hopefully these will require antiplatelet therapy for a short period of time only. Newer antiplatelet agents such as Ticagrelor are being developed. These agents cause reversible antagonism of platelet function and have a shorter duration of action than either Aspirin or Plavix. Hopefully these measures will make non-cardiac surgery for patients with coronary stents a safer option in the future.

References

1. **Maree AV, Fitzgerald DJ.** Aspirin and Coronary Artery Disease. *Thrombosis and Haemostasis* 2004; 92:1175-1181
2. **Spaulding C, Henry P, Teiger E et al.** Sirolimus – eluting stents versus uncoated stents in acute myocardial infarction. *New England Journal of Medicine* 2006; 355: 1-11
3. **Serruys PW, Kutryk MS, Ong AT** – Coronary Artery Stents. *New England Journal of Medicine* 2006; 354: 483-495
4. **Hovens MM et al.** Prevalence of Persistent Platelet Reactivity Despite Use of Aspirin : A Systematic Review. *American Heart Journal* 2007; 153: 175-181
5. **Grotemeyer KH et al.** – Two Year Follow Up of Aspirin Responder and Aspirin Non Responder. *Thrombosis Res.* 1993; 71: 397-403
6. **Lau WC et al.** Atorvastatin Reduces the Ability of Clopidogrel to Inhibit Platelet Aggregation: A New Drug-Drug Interaction. *Circulation* 2003; 107: 32-37
7. **Spartus JA et al.** Prevalence, Predictors and Outcomes of Premature Discontinuation of Thienopyridine Therapy After Drug-Eluting Stent Placement: Results from the Premier Registry. *Circulation* 2006; 113: 2803-2809
8. **Van Warkum JW, Heesermans AA, Zomer AC et al.** Predictors of Coronary Stent Thrombosis : The Dutch Stent Thrombosis Registry. *Journal American College Cardiology* 2009; 53: 1399
9. **Weisz G, Leon MB, Holmes Dr Jnr et al.** Five Year Follow Up After Sirolimus-Eluting Stent Implantation: Results of the Sirius Trial. *Journal American College of Cardiology* 2009; 53:1488
10. **Aoki J, Lansky AJ, Mehran R et al.** Early Stent Thrombosis in Patients with Acute Coronary Syndromes Treated with Drug-Eluting and Bare Metal Stents. *Circulation* 2009; 119: 687
11. **Seruys Patrick.** Resolute Allcomers Trial. EuroPCR Meeting 2010

2010 St Vincent's Clinic Foundation Grants

The Ladies' Committee Sr Mary Bernice Research Grant ***$100,000***

Chief Investigator: **Assoc Prof Reginald V N Lord**
Project: "Pharmacogenetic studies of cancer of the oesophagus"
Project Site: St Vincent's Centre for Applied Medical Research
Lay Description: *Development of genetic tests that can be used to guide more effective chemotherapy for patients with cancer of the oesophagus.*

Oesophageal cancer is increasing in incidence and is highly fatal. Previous studies indicate that various measurements of two genes, TS and ERCCI, are significant independent factors associated with response to standard chemotherapy drugs and thus patient outcomes including survival. In this study we will determine whether these genetic tests are clinically valuable for treating patients with oesophageal cancer.

Adult Stem Cell Research ***$100,000***

Chief Investigator: **Dr John Moore**
Project: "T-lymphocyte developmental restrictions of Adult Haematopoietic Stem Cells – relevance to transplantation and autoimmune disease"
Project Site: St Vincent's Hospital
Lay Description: *Exploring the ability of adult blood stem cells to increase their production of cells of the immune system*

Adult bone marrow is the primary tissue source for haemopoietic stem cells (HSCs) which reconstitute the immune system. T cells, an important part of the immune system, are slow to recover after transplant (ie for cancer treatment). We have found a method of treating adult HSCs which improves their yield of T cells. Characterization of the mechanism involved would open the possibility of treatment of cells to improve recovery after transplant, cancer therapy and autoimmune disease.

The Tancred Research Grant ***$50,000***

Chief Investigator: **Prof Bruce Brew**
Project: "Tryptophan metabolism in adult stem cell biology"
Project Site: St Vincent's Hospital
Lay Description:

The use of stem cells isolated from adult tissues holds promise as a novel therapeutic approach in multiple sclerosis (MS). This project seeks to optimize adult stem cell proliferation and differentiation to facilitate therapeutic transplantation for MS. Our existing results strongly suggest that metabolism of the essential amino acid tryptophan is a key factor controlling the ability of adult stem cells to proliferate and differentiate. We will use inhibitors of tryptophan metabolism in cell cultures and animal models to prove this. If correct, the results will considerably advance the therapeutic use of stem cells.

The K & A Collins Cancer Research Grant ***$50,000***

Chief Investigator: **Prof David Ma**
Project: "Prognostic value of novel biomarkers in the treatment of Ph+ leukaemia with tyrosine kinase inhibitors
Project Site: St Vincent's Centre for Applied Medical Research
Lay Description: *Novel gene markers to predict response to current anti-cancer drugs in patients with Philadelphia positive leukaemia*

Tyrosine kinase inhibitors are molecular targeted drugs which have revolutionised the treatment of Philadelphia positive leukaemia. These drugs are highly successful in controlling chronic forms of this leukaemia but ineffective against advanced cases. We aim to find out if the six biomarkers that we have discovered can predict the response of patients to therapy and identify who will develop resistance, thereby improving the cure rate of these patients.

The Di Boyd Cancer Research Grant ***$30,000***

Chief Investigator: **Dr David Williams**
Project: "Multi-disciplinary Pancreatic Cancer Screening Program of High Risk Groups"
Project Site: St Vincent's Hospital
Lay Description:

Pancreas cancer is a leading cause of cancer death. Since it is seldom diagnosed at an early curable stage, nearly all patients die of their disease. Early detection of pancreatic cancer and its precursors will save lives. Approximately 5-10% of all pancreatic cancers have familial aggregation and/or genetic susceptibility. Primary aim of this project is to establish a multi-disciplinary pancrease cancer screening service.

2010 St Vincent's Clinic Foundation Grants

The Froulop Vascular Research Grant ***$30,000***

Chief Investigator: **Assoc Prof Diane Fatkin**
Project: "Zebrafish models of atrial fibrillation"
Project Site: Victor Chang Cardiac Research Institute
Lay Description: *Zebrafish models of human heart rhythm disorders*

Atrial fibrillation (AF) is the most common heart rhythm disturbance and a major risk factor for stroke and heart failure. Inherited gene variations in families are an important cause of AF but exactly what these genes are, and the ways in which these changes can alter the heart's electrical activity and promote AF are not well understood. We are proposing to establish techniques to study the effects of gene variants identified in families with AF using genetically-modified zebrafish models.

Annual Award 1 ***$30,000***

Chief Investigator: **Assoc Prof Anthony Dodds**
Project: "The use of ultraviolet light photochemotherapy [PUVA] in the oral cavity in conjunction with an oral photo-sensitiser for oral graft-versus- host disease [GVHD] in allogeneic bone marrow transplant patients [ABMT]"
Project Site: St Vincent's Hospital
Lay Description:

Assessment of the safety and efficacy of oral Polarised UVA therapy after a oral photo-sensitiser (5-methoxypsolaren or 8-methoxypsolaren) in the treatment of oral Graft Versus Host Disease affecting the oral cavity post Allogeneic Stem Cell Transplant.
Patients eligible will have up to 40 treatments using a hand held PUVA lamp, delivering increasing doses through increased length of exposure.
All Patients will be offered treatment – there is no placebo arm treating CMV.

Annual Award 2 ***$30,000***

Chief Investigator: **Dr Mark Danta**
Project: "Liver Elastography in Cardiac Disease (LECD) study"
Project Site: St Vincent's Clinical School
Lay Description: *Non-invasive liver stiffness measurements to assess liver scarring in patients with cardiac failure*

Cardiac failure is often associated with congestion and inflammation of the liver, which can lead to scarring and cirrhosis. However, significant liver fibrosis can be very difficult to diagnose in cardiac failure as it presents with similar symptoms. Diagnosis often involves invasive test such as liver biopsy. A new ultrasound-based technology called Fibroscan has been developed which can assess liver fibrosis non-invasively. This study will evaluate the use of Fibroscan for liver disease in cardiac failure.

Annual Award 3 ***$30,000***

Chief Investigator: **Prof Terry Campbell**
Project: "The human-ether-a-go-go related gene K+ channel, a potential drug target for the treatment of schizophrenia"
Project Site: Victor Chang Cardiac Research Institute
Lay Description: *Investigation of a new treatment strategy for patients with schizophrenia*

Schizophrenia is a debilitating illness that is difficult to treat. Recently, it has been shown that a new ion channel protein is expressed at significantly higher levels in the brains of patients with schizophrenia. We will investigate whether it is possible to specifically target this new ion channel protein in the brain without having adverse effects on the heart that expresses a similar protein. If successful, this could pave the way for development of a new treatment for schizophrenia.

Annual Award 4 ***$30,000***

Chief Investigator: **Prof Ken Ho**
Project: "Significance of brown fat in humans"
Project Site: Garvan Institute of Medical Research
Lay Description:

The research concerns brown fat which, unlike ordinary 'white' fat, functions like heat generators, by burning fat, releasing energy as heat. It plays a major role in controlling body temperature and weight in animals. Contrary to what was believed, it has recently been discovered that significant amount of brown fat is present in adult humans. It can be readily detected using a type of nuclear medicine scan, positron-emission tomography, (PET_, widely used in clinical practice.
The nature, function and regulation of brown fat in adult humans is poorly understood. Our research aims to understand how brown fat is controlled in adult humans by using medications to stimulate brown fat activity on PET. The development of medications to stimulate brown fat activity is a potential way of treating obesity in the future.

2010 St Vincent's Clinic Foundation Grants

Annual Award 5 ***$30,000***

Chief Investigator: **Assoc Prof Jane McCrohon**
Project: "Prospective evaluation of cardiovascular biomarkers and the prognostic value of computer tomography coronary angiography"
Project Site: St Vincent's Hospital
Lay Description: *Assessing the risk of cardiovascular disease with blood markers and coronary CT*

Cardiovascular disease remains the major cause of death in Australia, however early diagnosis and selecting the appropriate time to commence treatment can prove difficult. This study involves setting up an online database to collect information and blood samples from people having cardiac CT scans. The information collected will help answer whether new blood tests can predict the extent of coronary disease.

Over the long term, the study will provide better information for people having coronary CT scans and provide new tools to give a more precise estimate of the individual risk of future heart attacks with and without treatment.

Annual Award 6 ***$30,000***

Chief Investigator: **Dr Jerry Greenfield**
Project: "Role of the autonomic nervous system in the development of obesity and type 2 diabetes mellitus"
Project Site: Garvan Institute of Medical Research
Lay Description:

Obesity and type-2 diabetes (T2D) are associated with alterations in the Autonomic Nervous System (ANS), which controls the automated nervous responses in the body. Obesity is associated with an impaired ANS response when stimulated using insulin. The question is whether changes in the ANS are a cause or a consequence of obesity. First-degree relatives of individuals with T2D (FDR) are at increased risk of developing T2D and obesity. We will study ANS function in FDR when they have normal sugar levels and are non-obese. We predict that these 'at risk' individuals have early changes in ANS activity that may contribute to later development of abdominal obesity and T2D.

Annual Award 7 ***$15,000***

Chief Investigator: **Dr Gonzalo Aguirrebarrena**
Project: "Diagnosis of penicillin allergy in the Emergency Department"
Project Site: St Vincent's Hospital
Lay Description:

This project aims to determine whether patients with true penicillin allergy can be detected in the Emergency Department setting, allowing a definitive diagnosis of penicillin allergy, improvement of a current or future antibiotic treatment, and lowering the antibiotic treatment cost-effective ratio.

Travelling Scholarship 1 ***$10 000*** ***Department of Neurosurgery***

Fellow: **Dr Mark Winder**
Post Graduate Study: *Complex Spine Fellowship, University of Calgary Canada & Skull Base Fellowship, Swedish Centre Seattle Washington Canada*

Travelling Scholarship 2 ***$10 000*** ***Department of Cardiology***

Fellow: **Dr Andrew Jabbour**
Post Graduate Study: *Cardiac Magnetic Resonance Clinical Research Fellowship at The Royal Brompton Hospital, London*

Travelling Scholarship 3 ***$10 000*** ***Department of Cardiology***

Fellow: **Dr Mark Perrin**
Post Graduate Study: *Electrophysiology Research Fellowship at Ottawa Heart Institute in Ottawa Ontario Canada*

Travelling Scholarship 4 ***$10 000*** ***Department of Cardiology***

Fellow: **Dr David Roy**
Post Graduate Study: *Interventional Cardiology Fellowship 2010-2011 at St Georges Hospital London*

2010 Multi-disciplinary Patient Focussed Research Grants

***Chief Investigator*: Mr Jed Duff** **$25,000**
***Project*:** "The PaMP VTE Trial (Patient Mediated Prevention of VTE Trial)
***Project Site*:** St Vincent's Private Hospital
***Project Summary*:** Venous thromboembolism (VTE) results significant mortality, morbidity, and healthcare resource expenditure. Despite the widespread availability of clinical guidelines clinicians still fail to provide their patiens with evidence-based prophylaxis measures. Implementation researchers have studied a number of strategies to increase guideline uptake. One strategy that has been shown to work in the primary care setting, but not previously studied in acute care, is patient-mediated interventions. This study examines the effect of a patient-mediated intervention on healthcare professionals' adherence to evidence-based VTE prevention guidelines.

***Chief Investigator*: Ms Melissa Brunner** **$25,000**
***Project*:** "Coordinated Multi-disciplinary Circuit Therapy Class"
***Project Site*:** St Vincent's Hospital
***Project Summary*:** Coordinated stroke unit care provides the best outcomes for stroke patients. One of the most important components of stroke unit care is early commencement of rehabilitation by a cohesive multidisciplinary team. The clinical guidelines for acute stroke care1 have made recommendations for best practice in acute stroke care, including assessments and interventions to be completed by team members. In order to ensure best practice standards of care are met, therapists need dedicated time and an efficient method for providing therapy.

Recent research has demonstrated the effectiveness of physiotherapy for stroke patients in a group circuit class format when compared to individual sessions2.

The aim of this before-and-after study is to determine the feasibility of conducting multidisciplinary therapy in a group circuit class on the acute stroke care unit. The study will compare process and outcome measures for acute stroke patients receiving standard multidisciplinary therapy with those who receive multidisciplinary therapy in a multidisciplinary circuit class. It will also examine patient and team satisfaction with this style of service delivery.

The current evidence in the literature has identified that this mode of service delivery has the potential to provide coordinated treatment with limited resources targeting physical function within the acute care setting3. The circuit class mode of service delivery has yet to be definitively evaluated utilising the multidisciplinary team and targeting all deficits post stroke (i.e. not just physical difficulties). With this in mind, the team are proposing that this will be a pilot study collecting preliminary data in preparation for running a definitive RCT examining patient outcomes within this type of care delivery structure in acute stroke.

***Chief Investigator*: Ms Fiona Bailey** **$25,000**
***Project*:** "Examining the management of reported medication incidents in an acute care hospital""
***Project Site*:** St Vincent's Hospital
***Project Summary*:** The aim of this pilot project is to gain an understanding of how medication incidents are managed at St Vincent's Hospital. Medication incidents are currently entered into an online incident reporting system, RiskMan, and it is then the role of the manager to manage a response to each incident. A literature review revealed deficiencies in how medication incidents are being managed globally. Reports indicate that no decrease in the actual numbers of medication incidents have occurred despite efforts to increase the voluntary reporting of medication incidents. In 2008, 772 medication incidents were reported at St Vincent's Hospital. In order to gain an understanding of how medication incidents are being managed, an audit and content analysis of the management strategies are reported by managers in the RiskMan will be undertaken for the period 1 January 2009 to 31 December 2009. Following the audit, two focus groups will be convened. The first focus group will include managers responsible for managing medication incidents. The aim of this focus group is to gain an understanding about what manager's regard as their role in managing medication incidents and to identify strategies to improve the management of incidents. The second focus group will involve clinical nurses and other staff members who report medication incidents, to ascertain what factors influence their willingness to report medication incidents and particularly to determine whether staff reporting of medication incidences is influenced by the manner in which the incidences are managed.

***Chief Investigator*: Dr Steven Faux** **$13,000**
***Project*:** "Patient outcomes from a group program for chronic pain at St Vincent's Campus Pain Service. How do they benchmark with those from an established intensive program at North Shore Hospital Pain Clinic?"
***Project Site*:** St Vincent's Hospital
***Project Summary*:** Exercise and Psychology based pain management programs are the treatment of choice for people with chronic pain which adversely affects their quality of life. There is a body of evidence indicating that pain management programs lead to improvements in pain experience, mood, coping, appraisal of pain, and activity levels. Pain programs are delivered as outpatient treatment or more intensive inpatient treatment. Whilst evidence suggests that more intensive programs lead to greater improvement, there is evidence that outpatient programs of a minimum of 30 hours lead to positive outcomes. There is also increasing recognition of the need to examine patient characteristics associated with positive outcomes from pain management programs and to examine which programs work best for which patients.

The primary aim of this study is to evaluate whether a 10 week group pain management program (80 hours) at St Vincent's leads to significant changes in measures of pain-related distress and disability, and whether it is of equal efficacy to more intensive programs (3 week fulltime 124 hrs).

The secondary objective is to examine which patient characteristics predict patient engagement to the program and positive outcomes from this program.