PROCEEDINGS

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EDITORIAL

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Editor, Proceedings

This 21st Issue of Proceedings sees return of the Sandra David Oration together with seven clinical articles, one of which (Drug-induced long QT syndrome) incorporates research undertaken under the auspices of a 2008 Sister Mary Bernice Research Grant.

The Sandra David Oration was given by Dr Malcolm Cook of the Lowy Institute for International Policy and Dr Cook discusses Australia's role in supporting development of small and fragile states in the South Pacific region.

Dr Vandenberg was the principal researcher in excellent work undertaken to understand the mechanism of induction of the potentially fatal (sudden cardiac death from arrhythmia) long QT syndrome by a variety of medications which might be innocently prescribed for coexistent cardiac disease or a number of (sometimes common) non-cardiac conditions. This work will lead to much more reliable assays to determine which drugs might potentially place patients at risk for development of arrhythmias such as the long QT syndrome. The work is a good example of the potential value that can be derived from funding research.

Despite the global financial crisis in 2009, the St Vincent's Clinic Foundation was actually able to increase the value of its annual grant applications for that year (see page 12). A total of $690,000 was spent, the Sr Mary Bernice Research Grant being awarded to Prof Ric Day for investigation into the optimum dose of Metformin in management of patients with adult onset diabetes mellitus. The money from the Sr Mary Bernice Research Grant is largely raised by the voluntary work of the Ladies' Committee of St Vincent's Private Hospital and Clinic.

On page 23 of Proceedings is an application form for those who might be interested in making a donation to assist with the continuing research work supervised by St Vincent's Clinic Foundation.

Drs Mukherjee and Aldred's article on "Deckled Incisions in facial surgery" is both innovative in concept and shows how basic research can be applied to new clinical approaches in order to determine their validity (or otherwise) as a continued form of treatment.

Associate Professor David Muller was the principal cardiac author in a paper describing a new technique wherein severe aortic stenosis (in frail elderly patients with comorbidities that would preclude open cardiac surgery) can now be treated by the percutaneous placement of one of two different aortic valve prostheses.

In our aging society, joint replacements are in increasing demand and Dr John Rooney, Orthopaedic Surgeon, describes his different and less invasive approach (in selected patients) to total hip joint replacement.

Drs Richard Harvey, Otolaryngologist, and Janet Rimmer, Respiratory Physician review the common condition of chronic rhinosinusitis including its surgical and medical management.

Macular degeneration is one of four major conditions affecting sight and in the developed world is the most common cause of irreversible visual loss in the elderly. In his article, Dr John Kennedy explains the mechanism for the wet and dry forms of macular degeneration and describes new treatment options which are changing the management of macular degeneration and providing new hope for those affected by it.

In the final article of this Issue, Dr Deepi Miller, a recently appointed psychiatrist to St Vincent's Clinic, describes current and future research work to further understand the inter-relationship between schizophrenia and substance abuse in our community.

Deckled Incisions in Facial Surgery

Dr Payal Mukherjee
Dr Russell Aldred

Introduction

The incidence of head and neck skin cancers is high in many western countries, as is the proportion of patients presenting for treatment of these lesions. While some superficial malignancies in non-critical areas may be suitable for a trial of topical treatment (cryotherapy, imiquimod etc.), surgery currently remains the "gold standard" for the treatment of skin cancers. In the hands of a qualified plastic surgeon, the recurrence rate after surgical excision of cutaneous malignancy is not high and the histopathologist usually readily identifies those few instances of incomplete removal. However, fear of a visible scar is sometimes the prime reason for a patient or practitioner to choose a less reliable topical measure, even when surgery is the most appropriate treatment.

Scar visibility is multifactorial. Skin closure technique is considered to play an important role. It is an established principle in plastic surgery that Z plasties[1] generally reduce scar contracture by breaking up the lines of tension in a wound. As an extension of this principle, it was postulated that irregular "deckled" (see below) skin incisions made during tumour excision and flap reconstruction would produce aesthetically superior scars. This study compares scar visibility in a population of patients who underwent a deckled skin closure with that of patients who had a conventional (non-deckled) wound closure.

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Derived from the description of the serrated edges of pages in certain fine books and stationery, the term "deckle" in surgery describes the making of a finely irregular skin incision, similar to a compact irregular sine wave (**Figure 1a**). Using a "15 degree" ophthalmic blade in a beaver handle held perpendicular to the skin edge, the margins of the specimen and the flap markings are incised in "deckled" fashion. A conventional No. 15 scalpel blade is then used to release the base of the specimen and to raise the base of the flap. The flap is sutured into the defect, without any attempt to align the serrations (deckles) with the opposing edges of skin. A deep layer of scanty 5.0 or 6.0 absorbable sutures is usually used, followed by 6.0 nylon surface sutures. The skin is closed in the usual manner, as if the deckles were not present at all. (**Figures 1b and 1c**).

A similar technique is used for the vermilion (**Figures 2a, 2b and 2c**).

Method

Scar analysis in two groups of patients was conducted at 4 to 8 months postoperatively. Of a sample of 47 patients contacted, attendance rate for follow up was 30%. 19 scars in 14 patients were examined. Nine scars were deckled and 10 were non-deckled – the latter comprising the control group. The patients had all undergone their operation at St. Vincent's

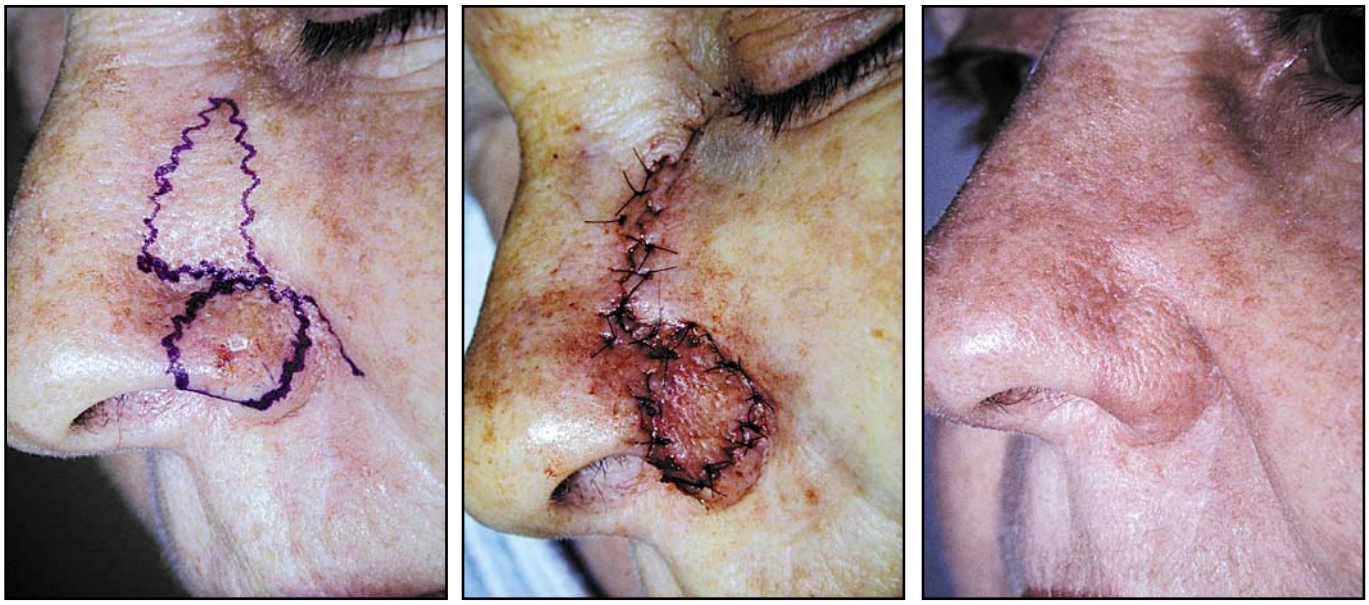
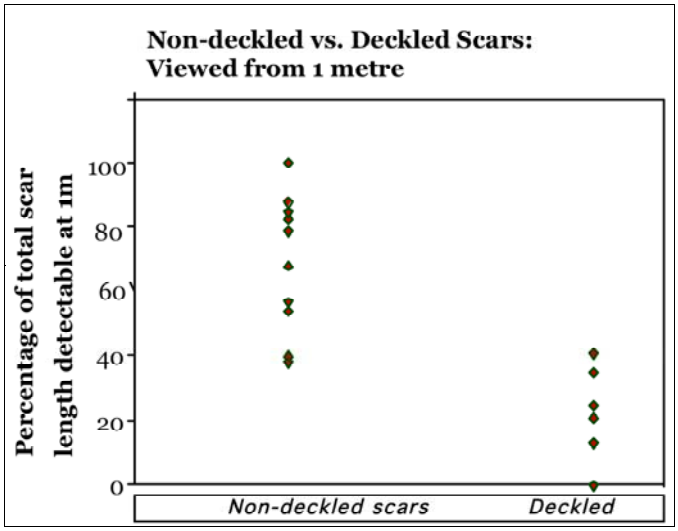


Figure 1a: *Basal cell carcinoma on the left ala of the nose with planned island flap repair, displaying the original "deckled" incision design, which sometimes resembled a W-plasty.* ***1b:*** *Immediately post-op. Meticulous alignment of the deckles during suturing is not necessary, but often occurs by chance.* ***1c:*** *Result at three months.*

Hospital by members of the plastic surgery department. The patients were examined in a double blind manner, in that the patients were unaware of the type of procedure they had received, as was the examiner. All scars were assessed by the same examiner, PM, to exclude any subjective variation between observers. Patients were all of Anglo-Saxon descent, had a history of only one procedure to the examined site, had all undergone skin flaps in the head and neck region and were all examined under standardised ambient conditions (same lighting, angle, distance and measurement tools). Scars were inspected at a distance of 1 metre and at then at 30 centimetres, and the length of detectable scar was measured for each nominated distance. This was expressed as a percentage of the total actual scar (traced out after review of operation reports and diagrams). The scar visibility percentages (ratios) were then compared between the two samples and statistical analysis was undertaken. Variables, in particular silicone gel sheet and tobacco use, were studied.

Results

Scar visibility was studied in the 2 samples both at 1 m and 30 cm (**Figure 3a and 3b**). The patients had an average age of 64 (range 37-89), and consisted of 5 female and 9 male patients. It was noted that there was a clear difference in the two groups, with the deckled



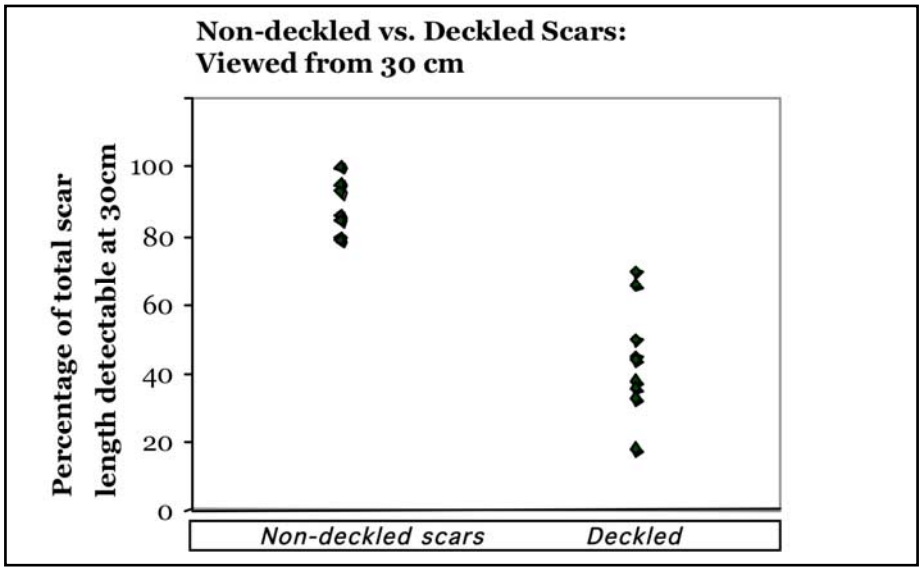


Figure 3a: *Assessment of scars at 1 metre;* ***3b:*** *assessment at 30 centimetres. The non-deckled group of patients displayed a more visible scar (higher scar percentage visibility) compared to the deckled group of patients. Note: overlapping scar ratios appear as one data point on the graph; hence 9 scars in the deckled group appears as 6 data points as there were 3 patients with 0% visibility and 2 with 13%. At the close-range assessment, there was a distinctive difference in the scar ratios for the two groups, with the deckled group displaying a more favourable scar visibility.*

patients exhibiting less detectable length of scar. That is to say, the deckled patients had a lower scar visibility ratio at both distant evaluation (1 m) and on closer inspection (30cm). Although the sample size was small, the difference was found to be statistically significant, with a p value less than 0.0001 (**Figure 4**).

Degree of tobacco use was studied to see if it adversely affected scar appearance. When plotted against scar ratio, it failed to show a trend in the studied subgroup of patients (**Figure 5**).

Silicone gel sheet usage was also recorded for the patients in both samples. None of the patients in the study used silicone gel sheet for the recommended therapeutic duration.[2] A total of 6 scars received silicone gel sheet, of which only 2 had gel sheet applied in excess of 5 days. Of these two patients, one commenced using it one month after her operation and then used it for 8 weeks. She attained scar ratios of 0 and 50 per cent at 1m and 30cm respectively, and had a deckled incision. Another patient, also in the deckled group, used it inconsistently for 6 weeks and then ceased. His scar ratios were 25 per cent and 45 per cent respectively.

Discussion

The principle of deckling first arose in the excision of head and neck lesions, particularly those around the nose. It was postulated in 1996 by the senior author, RA, that in dealing with skin flaps on the lower half of the nose, incisions into deep sweat gland territory may be responsible for the notorious grooved scar formation in these areas since a string of split glands could possibly heal as a furrow. It was felt that the resultant scars might be less perceptible if the incisions were made under magnification, meticulously avoiding all the deep, skin-lined sweat glands. Thus arose a fine irregular incision. With time however, despite due attention, it wasn't practical to avoid every sweat gland. Nevertheless, the scars still looked significantly better. The focus then changed to the irregular incision itself being the reason behind the favourable results. Over the next 12 years, the ideal size and shape of deckle was subsequently determined through trial and error and, for non-eyelid facial skin, was found to be a markedly serpentine or

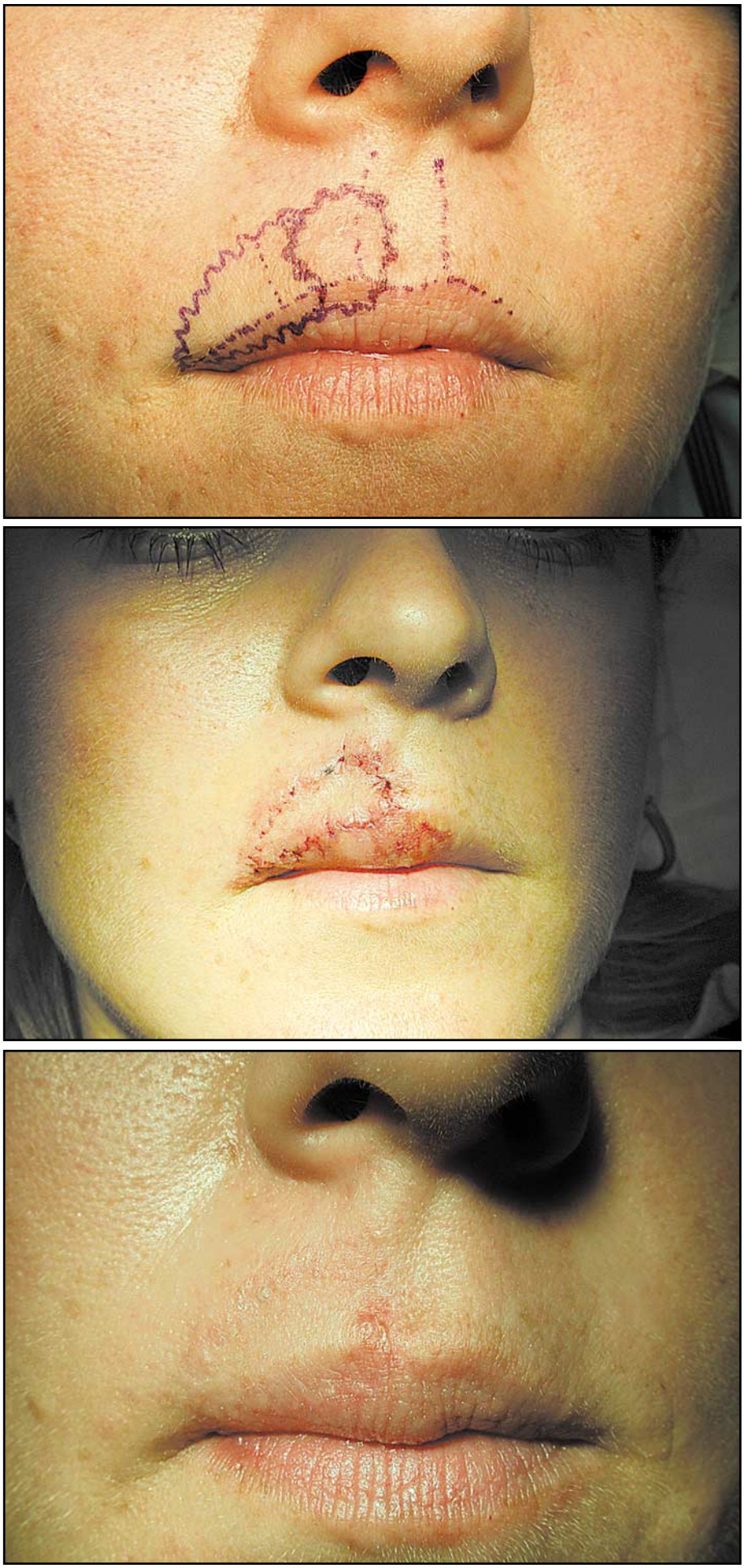


Figure 2a: *Deckled excision of basal cell carcinoma of the right philtrum of upper lip with planned flap repair;* ***2b:*** *appearance at suture removal after four days;* ***2c:*** *result at three months.*

meandering wave, two millimetres in amplitude.

The face and neck is the most expressive, most exposed part of a person. The cosmetic outcome of operations involving this area therefore plays a vital role in the patient's satisfaction with the operation. In addition, a wound that heals imperceptibly causes the patient less anguish, requires a lower frequency of follow up and imposes less pressure on the health system. While a novel technique may have its aesthetic advantages, it should be easy to apply, should not add greatly to operating time and should be reasonably consistent in its results.

The chosen mode of assessing the scar is also very important. Established objective assessment scales (such as the Vancouver scar scale), may have reliability and validity issues[3,4] and available scar assessment tools are not clinically feasible.[4] Furthermore, many such scales that study size, shape, texture, pigmentation and scar pliability are based on burns patients[7] and it is difficult to apply the same scar dynamics to facial elective surgical scars, large parts of which may not be visible at all to the un-aided eye. The present method was designed to address a sample of patients in whom scar visibility varied tremendously (0-100 per cent).

This study of a novel technique of surgery for cutaneous malignancies reveals that at both distant and close inspection, patients with deckled incisions had less visible scars than that of those who had conventional incisions. Single observer assessment of the scars produced results reproducible by other members of the team. When applied, the deckling technique produced consistently better results, adding only minimally (a minute or two) to the total time for the procedure. It is only in the making of the initial incision that operative time is slightly prolonged. The wound is closed in a conventional manner, with no additional time taken to align the deckles, although most peaks and troughs do coincidentally match up. The postoperative care of the wound is no different to that of conventional protocols. This is important in addressing compliance issues that may arise from confusing and complex postoperative orders.

Many studies have shown[5,6] smoking to be an important factor in the impedance of skin healing in a person. While this may be true per se, in this particular cohort of patients, there did not appear to be a rising trend when the degree of scar visibility was compared with degree of smoking (**Figure 5**).

Another variable studied was the use of silicone gel sheet. Silicone gel sheet, used fairly consistently for 3 months, has been shown to have beneficial effects on scar healing although there is some uncertainty about its mechanism of action.[2,7] Due to its sub-therapeutic use in the studied group of patients, its effect (if any) on the results is likely to be minimal. Continuing research needs to undertaken with larger samples of patients to ensure that the results attained from this study are consistently reproducible.

In our experience, the deckling technique is particularly effective for the nose and in fact anywhere on the face (**Figures 6a, 6b and 6c**). The cosmetic advantages of deckled incisions in operations on other parts of the body are not as great as those seen on the face. However, significant benefit may be observed provided that the deckle wave in the dermis is fairly contorted rather than subtle, and ideally it should be accompanied by some degree of over-correction of the closure using deep absorbable sutures.

Percentage assessment at

Group	1m	30cm
Deckle	16.4 (15.3)	44.4 (16.2)
Non Deckle	69.2 (21.2)	91.3 (8.2)
Difference	52.8 (18.7)	46.8 (12.6)
95% CI of difference	34.7, 70.8	34.6, 59
P value	<0.0001	<0.0001

Figure 4: *Average percentage of scar detectable at both 1m and 30cm assessment is displayed, with standard deviation in parentheses. Ninety-five percent confidence interval of the difference shows a positive difference. The difference is statistically significant with a p value <0.0001 at both distances.*

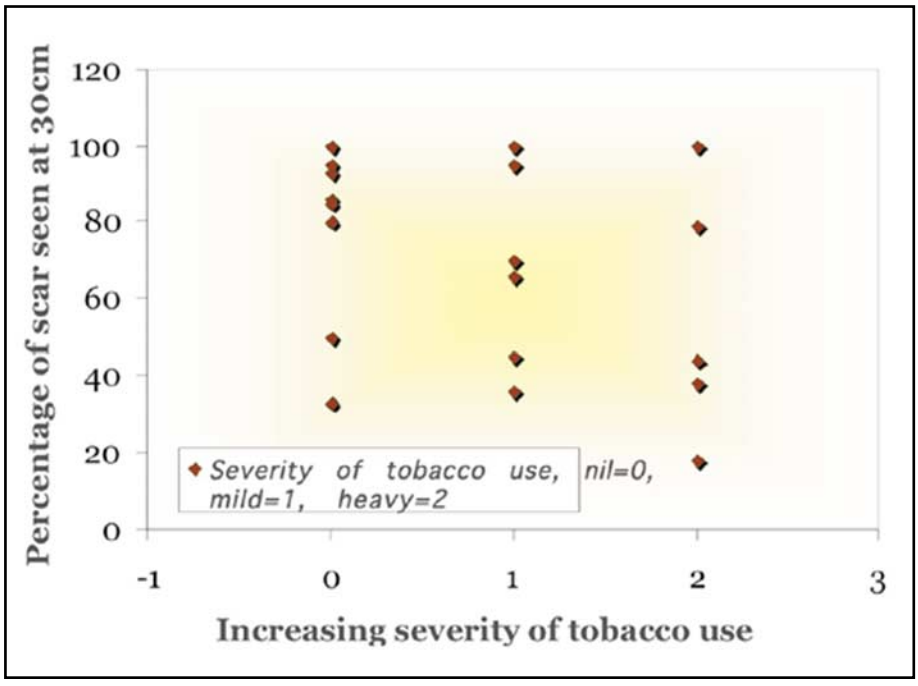


Figure 5: *Effect of smoking on scar percentage visibility.*

Conclusion

In this study, scar ratios/percentages were far lower at both 1 m and 30 cm in the "deckled" cohort, confirming that the aesthetics of deckled incisions are generally superior to those of straight incisions in facial surgery. This was a consistent finding despite multiple operators conducting the procedure. While smoking influences wound healing, and the use of silicone gel sheet probably has a favourable influence on scar visibility, these two factors did not conclusively affect the results in this particular sample.

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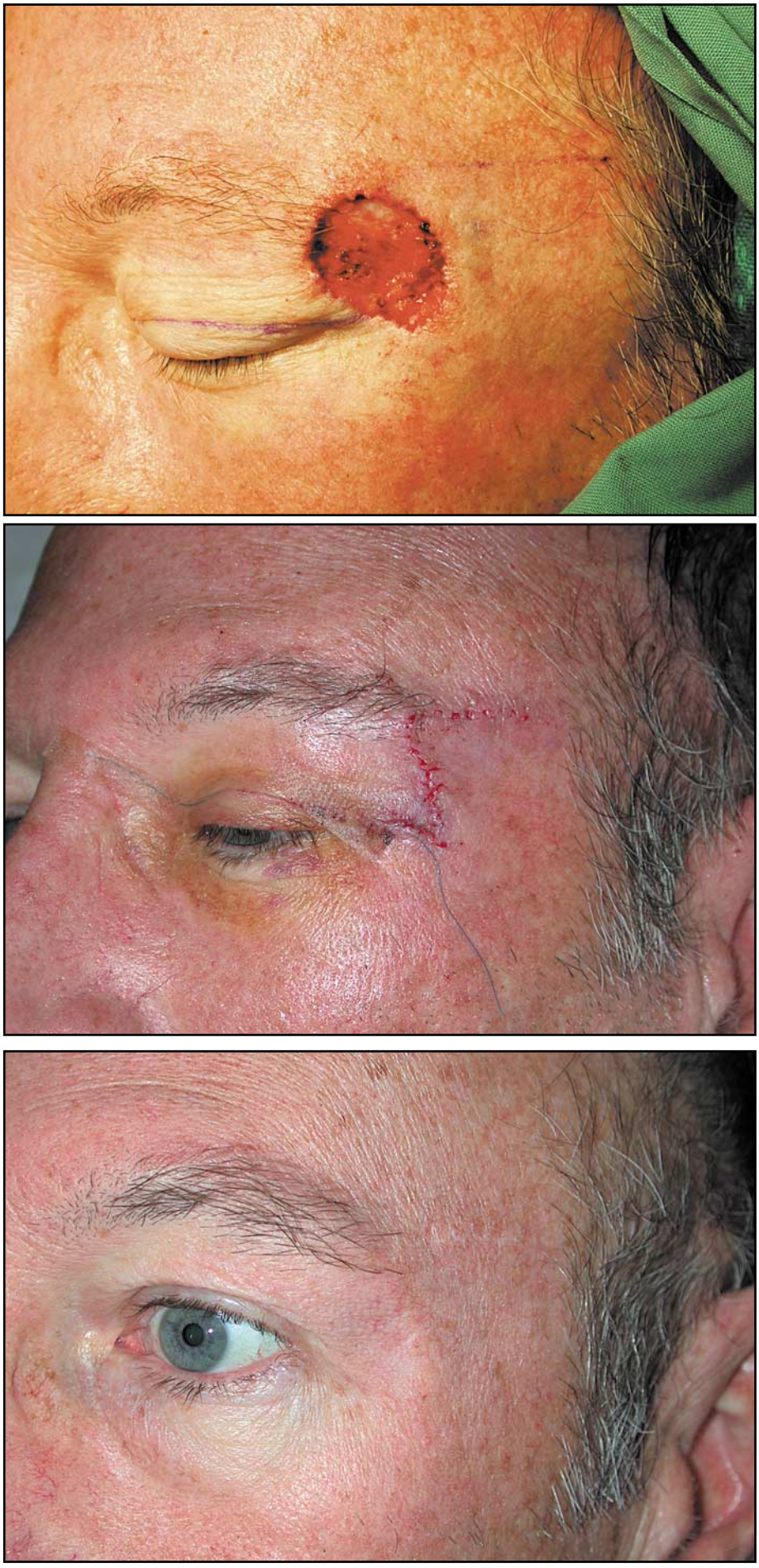

Figure 6a: *Wide excision melanoma-in-situ left upper eyelid with planned dual flap repair;* ***6b:*** *suture removal after 3 days;* ***6c:*** *appearance at 6 months. Deckled incision lines are often visible in parts, but usually blend with skin texture.*

Percutaneous Management of Aortic Valve Stenosis

David Muller
David Baron
Paul Roy

Degenerative aortic valve stenosis is a common condition in the elderly with an estimated prevalence of approximately 4.5 per cent in individuals greater than 75years.[1] Without treatment, patients with symptomatic, severe aortic stenosis have a high morbidity and mortality with an estimated 2 year survival rate of less then 50 per cent.[2] Conventional treatment for the condition is surgical aortic valve replacement which is highly effective in low risk patients. However, the risk increases considerably in elderly patients with co-morbidities such as left ventricular dysfunction, chronic renal impairment, chronic lung disease, and cerebrovascular disease.[2] The surgical mortality doubles in patients who require concomitant coronary bypass graft surgery. In one large US registry, the surgical mortality was approximately 3.5-4.5 per cent in patients having valve replacement alone, and 6.5-7.0 per cent in patients who required concomitant coronary surgery.[3] Outcomes are also highly dependent on operator and institutional volume with mortality rates as high as 13 per cent in low volume centres.[4]

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Until recently, treatment options have been limited for patients considered to be at high risk for adverse peri-operative outcomes. It has been estimated that at least 30 per cent of the elderly population with aortic stenosis who meet AHA/ACC guidelines for surgical intervention are not offered surgery because of their co-morbidities or advanced age.[5] Other patients refuse surgery because of the prolonged recovery period. Some years ago, balloon valvuloplasty was performed in these patients as palliative treatment but the procedure was largely abandoned because of the limited short term efficacy and high peri-procedural vascular morbidity.[6]

The concept of percutaneous valve implantation was described more than 35 years ago but is was not until 2002 that the first human aortic valve implant was performed.[7] In contrast to surgical valve replacement, percutaneous valve implantation does not require a median sternotomy or cardiopulmonary bypass, and does not involve removal of the native valve leaflets. After balloon dilatation of the stenotic valve, a delivery catheter is advanced from the access site and the prosthesis is deployed within the aortic annulus, pushing aside the leaflets of the diseased valve. Since 2002, the procedure has evolved rapidly. Two devices received regulatory approval (CE Mark) in Europe in 2008 and since then, the number of valve implantations has increased exponentially. More than 8,000 valves had been implanted globally by mid 2009.

At St Vincent's Hospital, the first percutaneous aortic valve implantation was performed in August 2008. We are now one of few sites globally to have experience with both the devices that have CE Mark approval. Since neither of the devices has been approved for commercial use by the Australian Therapeutic Goods Administration (TGA), the procedures are performed under a research protocol with the approval of the St Vincent's Hospital Human Research Ethics Committee.

Prior to valve implantation using either device, a rigorous evaluation is performed to minimise the risk of peri-procedural morbidity. To be eligible for the procedure, patients must have severe aortic valve stenosis and be at high risk for surgery due to their advanced age or co-morbidities such as chronic lung disease, pulmonary hypertension, previous cardiac surgery, or previous thoracic radiation or burns (**Tables 1, 2**). Measurements are made of the aortic valve annulus, sinuses of Valsalva, ascending aorta and iliofemoral vessels to ensure that they are anatomically suited to the procedure. Patients are excluded from eligibility if they have

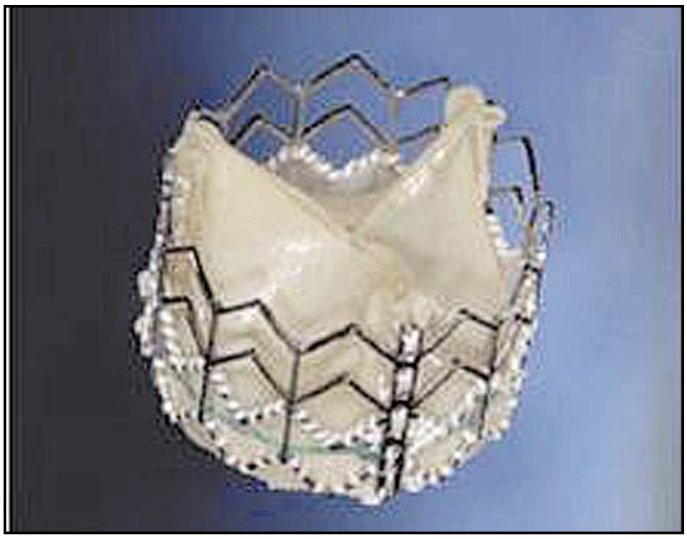

Figure 1: *The Edwards Sapien balloon expandable aortic valve.*

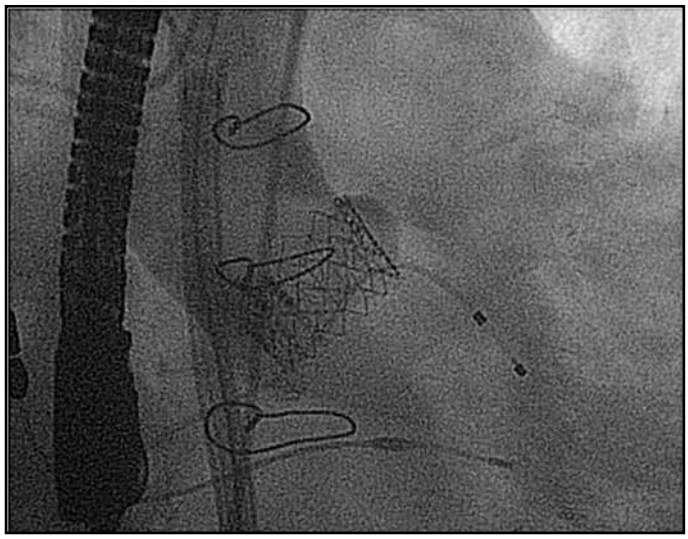

Figure 2: *Edwards Sapien aortic valve prosthesis after implantation.*

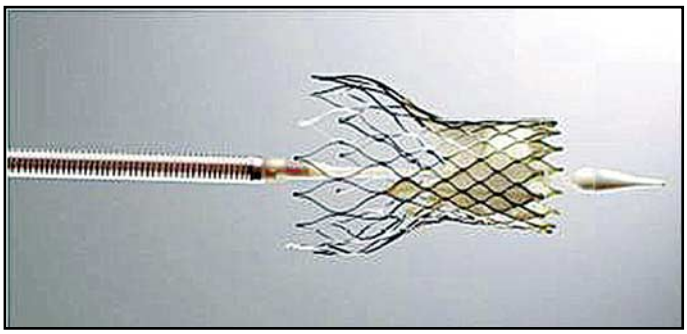

Figure 3: *The self-expanding Medtronic CoreValve device.*

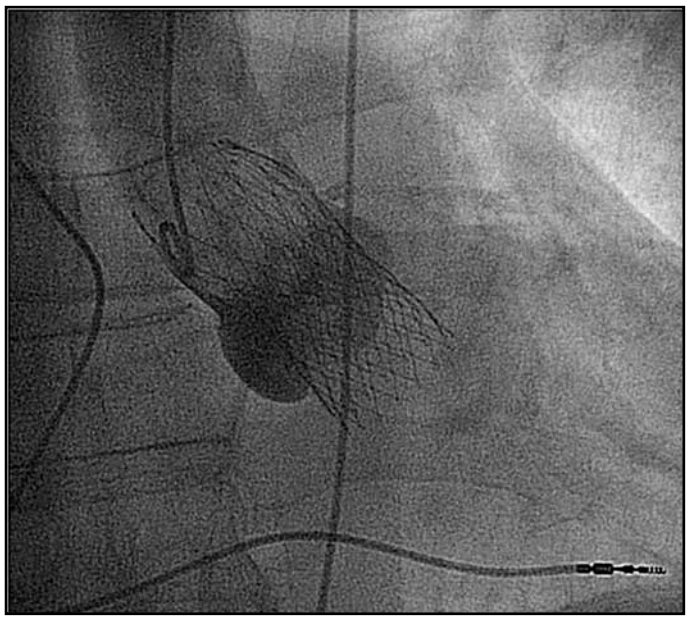

Figure 4: *A Medtronic CoreValve prosthesis in situ.*

poor left ventricular function, poor renal function, severe mitral regurgitation, or severe left ventriuclar hypertrophy (**Tables 3, 4**).

Edwards Sapien Valve

The first aortic valve implanted clinically was a balloon expandable device that was delivered via an antegrade, transseptal route.[7] Several modifications have been made to this device which now consists of a stainless steel frame and a valve constructed from bovine pericardium (**Figure 1**). The device is similar conceptually to valves implanted surgically. Two sizes are currently available, a 23mm device for annular sizes from 18 to 22mm, and a 26mm device for annular sizes from 21-25mm. The 23mm device is deployed through a 22F delivery sheath. The larger device requires a 24F delivery sheath. As a consequence of the large diameter of the delivery sheath, patients with femoral artery diameters <7mm are not eligible for transfemoral delivery. A minimum arterial diameter of 8mm is required for the 24Fr system. Patients with heavily calcified and tortuous iliofemoral vessels are poor candidiates for this approach. For these patients, a transapical approach may be considered. This requires a left lateral mini-thoracotomy and direct puncture of the left ventricular apex. It is anticipated that an 18F delivery system will be available in Australia in mid 2010.

Once positioned appropriately, the device is deployed by balloon inflation while the right ventricle is paced rapidly for 10-15sec to reduce the cardiac output, thereby minimising movement of the valve during implantation. Transoesophageal echocardiography and general anaesthesia are usually employed to optimise positioning of the device which should lie within the annulus and below the coronary arteries (**Figure 2**).

CoreValve Prosthesis

Whereas the Edwards Sapien valve is balloon expandable, the CoreValve prosthesis is a self-expanding nitinol frame that has thermal memory properties (**Figure 3**). A three leaflet valve constructed from porcine pericardium is sewn into the lower third of the device. When fully deployed, the upper third of the device is in contact with the wall of the ascending aorta (**Figure 4**). It has a low radial force and is responsible for ensuring the correct alignment of the device. The central third of the device contains the valve leaflets. Its concave shape is designed to minimise interference with coronary flow. The lower third of the device has a very high radial strength that anchors the device in the annulus.

The device is initially assembled in iced water which allows it to be constrained on a delivery catheter. It is deployed by gradual retraction of the retaining sheath which allows the device to expand at body temperature to its original conformation. The initial clinical experience was obtained with a 25F system that required surgical exposure of the femoral artery. Technological improvements in the device have reduced its profile to an 18F system, with a corresponding increase in patient eligibility, and reduction in vascular morbidity. Patients with femoral artery diameters greater than 6.0mm may be considered for the procedure. Two sizes of the device are currently available, a 26mm device for annular diameters of 20-23mm, and a 29mm device for diameters from 24-27mm.

Clinical Outcomes

The major complications of percutaneous aortic valve implantation include arterial injury, wire perforation of the left ventricle and pericardial tamponade, coronary occlusion and myocardial infarction, device embolisation, and stroke. Paravalvular aortic regurgitation is common and is due to incomplete apposition of the valve frame to the annulus because of the continued presence of the bulky native leaflets. Advanced AV block requiring permanent pacemaker implantation occurs infrequently with the Edwards Sapien device but is more common after use of the CoreValve device.

a) Edwards Sapien valve:

Clinical outcome data were recently published for a population of 168 patients who were treated with the Edwards Sapien device. One third of these patients had transapical valve implantation procedures.[8] The median age was 84yrs. The procedural mortality rate was 1.2 per cent, and the 30 day mortality rate was 11.3 per cent. The mortality rate at 30 days was higher for the transapical procedures than for the transfemoral valve implantations (18.2 per cent vs 8.0 per cent). This difference is likely to reflect the greater co-mordidities and higher risk of patients

Table 1. *Inclusion Criteria for Edwards Sapien PAVR Candidates*

Aortic valve area <0.8cm2; annulus diameter 18-25mm
Euroscore ≥ 20 per cent and STS score>10 per cent OR
Non-operable for surgical AVR

Table 2. *Inclusion Criteria for CoreValve PAVR Candidates*

Euroscore ≥ 20 per cent
Age ≥ 80 years
Age > 65 years with one major co-morbidity (hepatic cirrhosis, pulmonary insufficiency, previous cardiac surgery, porcelain aorta, pulmonary hypertension >60mmHg, recurrent pulmonary emboli, RV insufficiency, thoracic deformity or extensive burns, mediastinal radiation, severe connective tissue disease)

Table 3. *Exclusion Criteria for Edwards Sapien PAVR Candidates*

Non-valvular or congenital aortic stenosis
Intracardiac mass, thrombus or vegetation; bacterial endocarditis
Untreated proximal coronary stenoses
Unstable angina, or acute MI within one month; recent CVA
Aortic annulus diameter < 18mm or > 25mm
Bulky calcified aortic leaflets
Inadequate height of coronary ostia above leaflets
Left ventricular ejection fraction < 20 per cent
Ilio-femoral vessel diameter < 7mm*
Bilateral iliofemoral bypasses, or severe iliofemoral calcification/tortuosity*
**for transfemoral delivery*

Table 4. *Exclusion Criteria for CoreValve PAVR Candidates*

Left ventricular ejection fraction < 20 per cent
Mitral Regurgitation > Grade 2+
Atrial or ventricular thrombus present
Severe left ventricular hypertrophy (wall thickness > 17 mm)
Presence of sub-aortic stenosis
Aortic annulus diameter < 20 mm or > 27 m
Aortic root diameter < 27 mm
Height of coronary ostia above leaflets
< 10 mm without calcification
< 13 mm with moderate calcification
< 14 mm with severe calcification
Untreated proximal coronary stenoses
Annulus to aorta angle > 70 degrees
Ascending aortic diameter > 43 mm
Highly angulated aortic arch
Moderate to severe aorto-iliac disease
Ilio-femoral vessel diameter < 6 mm

selected for the transapical approach. The stroke rate for the total population was 4.2 per cent, and major vascular injury occurred in 6.6 per cent.[8] Further data will soon be available from the North American randomised trial (PARTNER) which compared percutaneous valve implantation with surgical valve replacement in surgically eligible patients, and with medical therapy in patients who were ineligible for surgery.

b) CoreValve prosthesis:

Unpublished data from more than 1200 high risk patients treated with the CoreValve device prior to November 2008 show a procedural mortality of 1.7 per cent, a 30 day mortality of 6.7 per cent, and a stroke rate of 1.7 per cent.[9] The most frequent complication has been the need for permanent pacemaker implantation for advanced AV block, a complication thought to be related to pressure of the self expanding device on the underlying conduction pathways. In most centres, the need for pacemaker implantation has been approximately 30 per cent. These data are similar to those reported for the early Australia and New Zealand experience which was recently reported.[10] In six centres, 123 high risk patients aged 82.3+7.7yrs were treated over a 12 month period. The procedural success was 98.4 per cent, and 97.1 per cent of the patients were discharged alive and well from hospital. There were no procedural deaths; 30 day all cause mortality was 4.3 per cent, and the cardiac mortality was 3.2 per cent. The incidence of stroke was 4.3 per cent; 35 per cent required implantation of a permanent pacemaker. At 30 days, the peak aortic valve gradient had fallen from 76+26mmHg to 16+7mmHg, and 84 per cent of the patients had improved clinically by at least one NYHA grade. Mild or moderate paravalvular aortic regurgitation was present in 34 per cent of the patients.

Summary

Percutaneous aortic valve implantation is a viable option for the management of severe aortic valve stenosis in patients who are inoperable or have a high risk of an adverse peri-operative outcome from conventional open heart surgery. Because these devices are not yet approved by the TGA and consequently, not funded by Medicare or the health insurance funds, the number of patients who can be offered this therapy is limited. In carefully selected patients, excellent haemodynamic and clinical results can be achieved with a low risk of major adverse events. It is likely that the procedure will be cost effective when compared with high risk cardiac surgery, or prolonged medical therapy for the management of congestive cardiac failure. Future developments will allow the application of this approach to be extended to a greater proportion of the elderly population and perhaps, eventually, to patients who are otherwise eligible for conventional open heart valve replacement surgery.

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2009 St Vincent's Clinic Foundation Grants

The Ladies' Committee Sr Mary Bernice Research Grant – $100 000
St Vincent's Hospital – ***Prof Richard Day***
"Optimising Metformin dosing regimens in patients with diabetes"

Adult Stem Cell Research Grant – $100 000
Victor Chang Cardiac Research Institute – ***Prof Richard Harvey***
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The Tancred Research Grant – $50 000
St Vincent's Hospital – ***Dr Richard Hillman***
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The Froulop Vascular Research Grant – $40 000
Victor Chang Cardiac Research Institute – ***Prof Peter Macdonald & Dr Paul Jansz***
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"Involvement of the kynurenine pathway in the persistence of brain tumours"

Annual Awards –

1. St Vincent's Hospital – ***Dr Lewis Campbell & Assoc Prof Debbie Marriott*** ($30 000)
   "Reactivation of cytomegalovirus in the critically ill patient: is it an important cause of morbidity and mortality in the Intensive Care setting?"
2. St Vincent's Clinic School – ***Dr Mark Danta*** ($30 000)
   "Permucosal transmission of hepatitis C virus in high-risk populations"
3. Victor Chang Cardiac Research Institute – ***Assoc Prof Diane Fatkin*** ($30 000)
   "Atrial endocardial endothelium: a substrate for atrial fibrillation?"
4. St Vincent's Hospital – ***Assoc Prof Christopher Hayward*** ($30 000)
   "Comparison of anti-platelet therapies on left ventricular structure and function in severe congestive heart failure"
5. St Vincent's Hospital – ***Dr Rajesh Subbiah*** ($30 000)
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6. St Vincent's Hospital – ***Dr David Brown*** ($30 000)
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"Orthopaedic Rehabilitation Outcome Comparison"

Anterior Minimally Invasive Surgery-Total Hip Arthroplasty

Dr John Rooney

Introduction

Osteoarthritis (OA) is the commonest form of arthritis in our population.[1] As our nation ages, its prevalence and relevance is becoming increasingly more important to our community.

The Australian Orthopaedic Association National Joint Replacement Registry, reported in 2008 that 31,333 conventional and revision total hip replacements were performed in Australia.[2] Total hip arthroplasty (THA) has been well established over the last 25 years and traditionally hip replacement surgery involves a posterior or lateral approach. However, in the past decade minimally invasive joint replacement of the hip has gained in popularity.

During my Post Fellowship training at the St Michael's Hospital, University of Toronto, I gained first hand experience and closely followed the developing trend of computer assisted surgery (CAS). In combination with minimally invasive THA using a Direct Anterior Approach (DAA) I have worked with some of the leading surgeons in this field. Following thorough research into the combination of the DAA and CAS, I have successfully introduced this technique into my practice for those appropriate patients.

This article briefly reviews the procedure including the use of CAS, the prosthetic design and the reported outcomes.

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Orthopaedic Surgeon
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The Procedure

The basic premise of minimally invasive hip surgery is to minimise the soft tissue disruption. Anterior minimally invasive surgery total hip arthroplasty using the DAA has been in practice since 2005.[3] The skin incision is small, approximately eight to 10cm in length (**Figure 1**) compared to the traditional 15-20cm with other approaches. The design of special instruments has allowed this evolution in minimally invasive surgery as it minimises soft tissue damage and importantly allows no muscle to be cut (**Figure 2 & Figure 3**). The procedure can be performed with or without the use of a traction table which has both its disadvantages and advantages.

Anterior minimally invasive surgery via the DAA has many benefits: a small anterior incision, minimal blood loss, no muscle is cut or compromised, less analgesia is required, and the patient has a quicker recovery leading to a shorter hospital length of stay with minimal hip precautions. The DAA technique has been shown to be suitable for primary and revision hip surgery as well as fractures of the femoral neck and therefore it is available to the vast majority of our hip patients.[3-8]

Computer Assisted Total Hip Surgery

Computer assisted surgery in total hip arthroplasty is an intra-operative tool to assist the surgeon with data to achieve the optimal implant position for the individual patient.[9] CAS is now common in orthopaedic surgery,[10-21] Leading surgeons in both Europe and North America have combined DAA with computer assisted surgery when undertaking a total hip replacement resulting in improved outcomes.

The smaller incisions used in a DAA, combined with computer assisted navigation (**Figure 4**) provides a more

accurate method in which to place the components with greater reproducible precision.[10, 12, 16, 19-21] Masonis et al (2008) performed a retrospective review on a single surgeon's initial consecutive series of THAs performed via a DAA. They found that measured parameters of cup abduction angle, dislocation rate, and leg length discrepancy were excellent.[5] Intra-operative radiographic imaging has been traditionally used in DAA, however the use of CAS has decreased this necessity.

The DAA with CAS gives the surgeon an added advantage to reconstruct hip joint biomechanics[5, 22] with excellent hip range of motion, a reduced dislocation rate[23] and the ability to minimise the risk of leg length inequality.[22]

Prosthesis Design for the Younger Patient

With a conventional femoral prosthesis hip design, the size and anchoring of the stem will result in a significant loss of bone mass due to the volume of the prosthesis and to frequent stress shielding.[24]

In younger patients particularly, this is a drawback in view of a possible exchange of the prosthesis in the future.[24] The conventional femoral prosthesis hip stem was redesigned to decrease its size and the principle of fixation changed to metaphyseal anchoring .[24] This has led to short femoral stem prostheses.

A short femoral stem prosthesis can be an attractive alternative to hip resurfacing arthroplasty in the same selected patients[4] and will fulfill their requirements in terms of quality of life and mobility in everyday life.[25,26] The early clinical and radiographic results have demonstrated good outcomes.[25,26] Combined with minimally invasive techniques, these implants allow preservation of muscle and bone stock without introducing some of the complications, such as femoral neck fracture, associated with resurfacing implants.[4]

Short femoral stem components combined with the DAA have three key advantages: it is as minimally invasive as possible; it has a modular design; and has

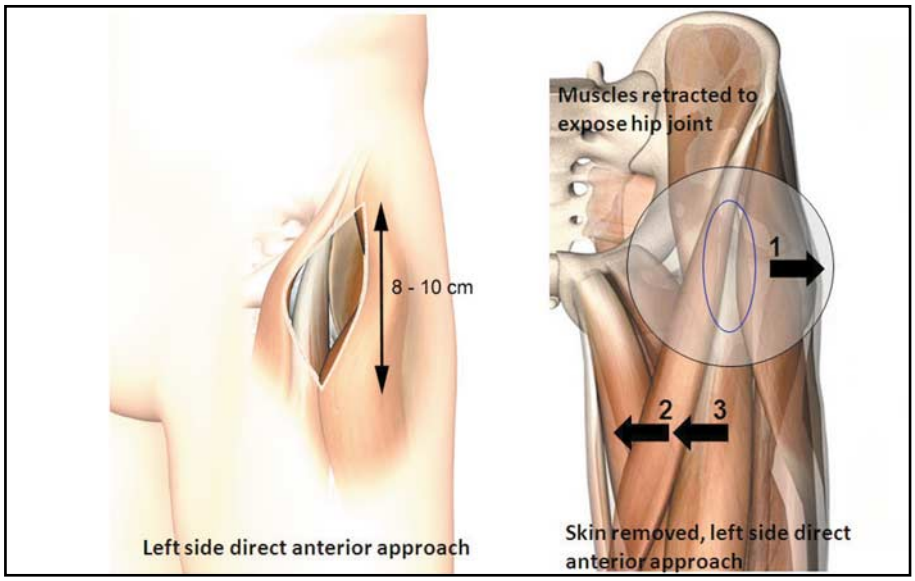

Figure 1: *Small incision and* ***Figure 2:*** *Muscles retracted and no muscles cut*

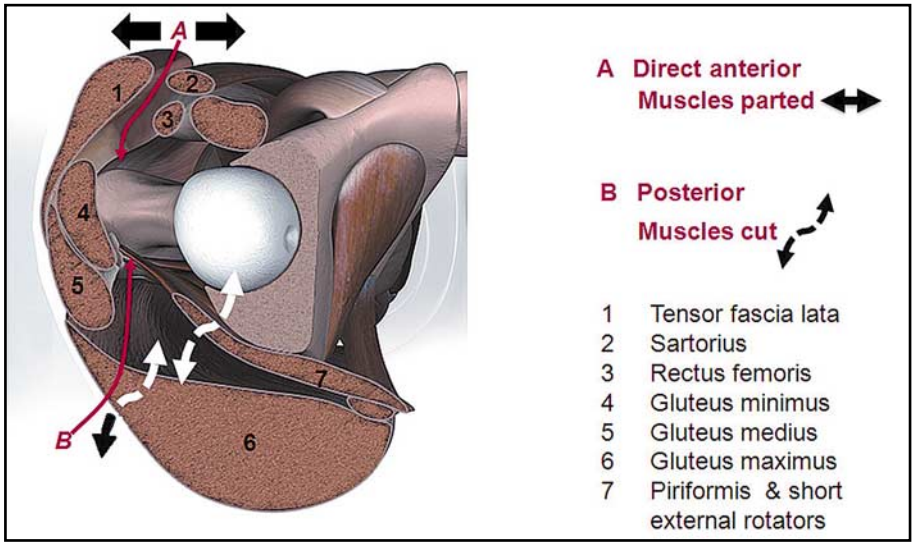

Figure 3: *Cross section of anterior and posterior approaches to the hip joint*

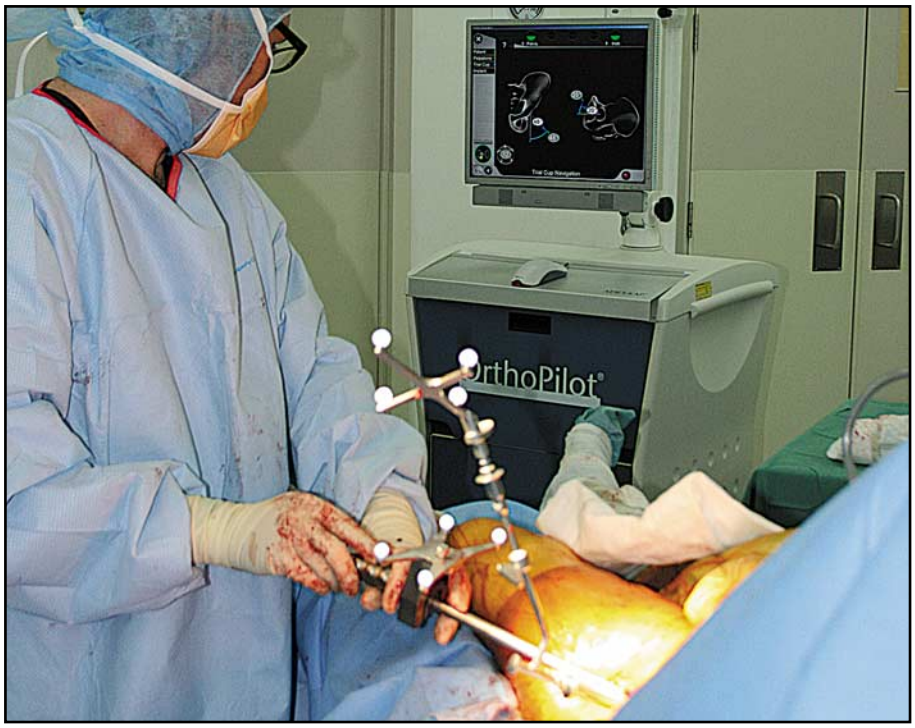

Figure 4: *Intra-operative Orthopilot navigation screen illustrating detection of reference frames*

minimal stem size that preserves bone stock. The modularity of the short stem allows for patient specific anatomical requirements and using the DAA approach the latest technology and techniques are applied. Thus short stem implants are introduced with preservation of bone, soft tissue and muscle. **Figure 5** shows a pre-operative diseased hip joint and **Figure 6** joint replacements utilising the conventional as opposed to the short modular femoral stems.

Results via Direct Anterior Approach

In 2008 Nakata et al classified 182 consecutive patients (195 hips) treated by primary cementless minimally invasive total hip arthroplasty (THA) into 2 groups via the surgical approach: group 1 (DAA-99 hips) and group 2 (mini-posterior approach-96 hips). Nakata's study showed a more rapid recovery for hip function and gait ability after DAA when compared to the mini-posterior approach. The study also found that DAA facilitated quicker and better recoveries as measured by single leg stance, walking time and the use of assistive walking aids.[6] Reassuringly, Rachbauer et al (2005) also concluded that the DAA technique was safe, reduced soft tissue damage, led to accelerated recovery and blood loss was minimal.[3]

Recent reports have found that the use of direct anterior approach for total hip arthroplasty have shown a lower dislocation rate and early functional recovery. Jayankura et al (2009) found that the DAA is a muscle-sparing procedure which theoretically ensures a fast recovery and in comparison to other studies with the same design of THA after posterior and particularly lateral approaches, muscle strength recovery seems to be faster and more complete with the DAA.[27] Finally, in another recent study by Oinuma et al (2009), it was found that the DAA provides immediate stability to the hip, decreasing dislocations associated with the release of muscles and therefore a reduced rate of postoperative dislocation.[28] Siguier et al (2004) reported a dislocation rate of 0.96 (10 out of 1037 cases) following computer assisted surgery.[29]

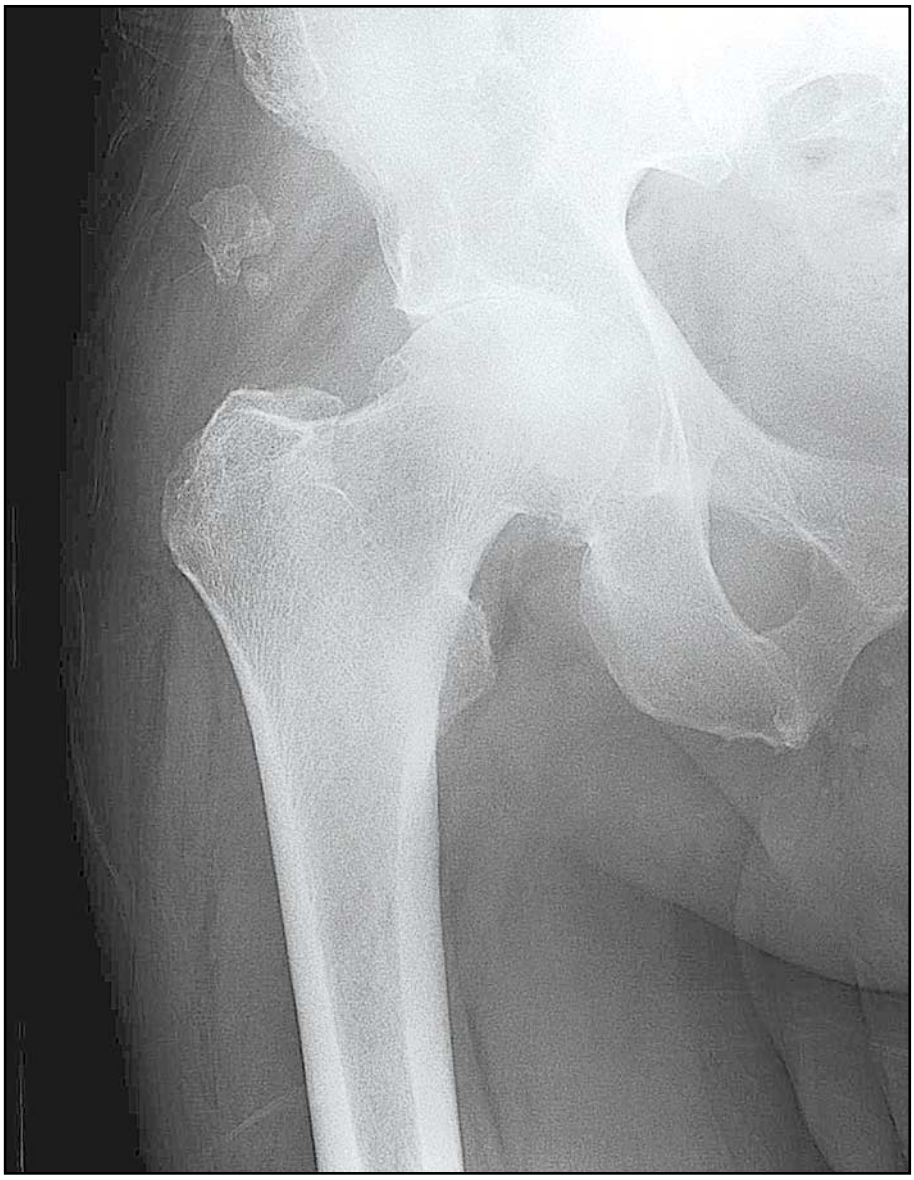

Figure 5: *Radiograph of a pre-operative diseased hip joint*

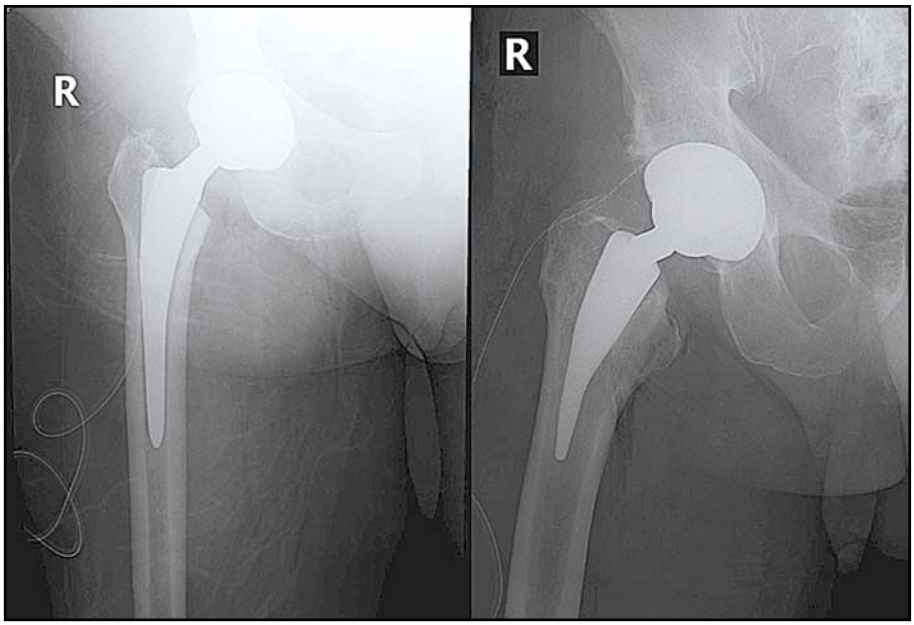

Figure 6: *Radiograph of the conventional and short modular femoral stems*

Summary

The DAA avoids any nonessential tissue dissection and allows easier access to the diseased hip joint which results in lower morbidity and rapid rehabilitation. The use of a short stem design, also allows for the maintenance of bone stock if revision becomes necessary in the future. The DAA method in combination with CAS is a safe procedure that allows correct placement of acetabular and femoral components. It is performed in a reasonable time, with minimal blood loss and in particular, the procedure preserves the muscles and leads to small, aesthetic scars.[7] By using computer assisted surgery DAA surgical interventions are further enhanced leading to better outcomes. The DAA approach is highly advantageous because it minimises interference with physiology, lifestyle and future treatment options.

Acknowledgements

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Chronic Rhinosinusitis: current concepts

Richard Harvey
Janet Rimmer

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disorder of the nose and sinuses which clinically is defined as persistence of symptoms for at least 12 weeks of nasal blockage or discharge combined with endoscopic abnormalities (polyps, mucopurulent discharge, mucosal swelling) or abnormal sinus CT scan. Other symptoms may include facial pain or reduced sense of smell.[1]

While allergy and bacterial infection play a role in the aetiology of this condition it is best considered to be a multifactorial chronic inflammatory disorder. It is distinguished from allergic rhinitis by the involvement of both the nose and the sinuses. The lower respiratory tract is frequently affected as well supporting the concept of united airways disease.[2] CRS affects an increasing proportion of the adult population until the sixth decade then declines.[3]

CRS is thought to affect between five per cent and 15 per cent of the population.[4] It is a diagnosis that is made by a wide variety of practitioners, including primary care physicians, otolaryngologists, immunologists, allergists and respiratory physicians. It is the principal diagnosis in nearly two per cent of all patient visits to primary care.[5]

CRS has a significant impact on the quality of life and health burden within the adult population.[6] The impact of the disease on quality of life, as measured by SF-36 scores, is comparable to or worse than that of other chronic conditions such as chronic obstructive pulmonary disease, congestive heart failure and back pain.[7]

Medical therapy has been the basis for treating chronic rhinosinusitis. Short and long-term antibiotic therapy, topical and systemic steroids, topical and oral decongestants, oral antihistamines, mast cell stabilisers, anti-leukotriene agents, mucolytics, topical antibiotics, topical and systemic antimycotics, proton pump inhibitors, bacterial lysates, immunotherapy, phytotherapy and avoidance of environmental factors have all played a role in management.[1]

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Shifting Concepts in the Pathogenesis of Chronic Rhinosinusitis

The inflammatory changes of CRS (including nasal polyps) represent a common endpoint of several potentially coexisting pathologic factors. What mediates this prolonged inflammatory mucosal response? Even though allergy has always been implicated, evidence that atopy predisposes to chronic or acute rhinosinusitis is still lacking.[8,9] Other pathologic aetiologies in CRS include ciliary dysfunction, immune deficiency, ostial obstruction, bacteria, fungi, super-antigens (ie. exotoxins), leukotriene abnormalities, , biofilms,[10] osteitis and environmental factors.[8,11] A multifactorial pathogenesis of CRS seems likely (**Figure 1**). There is significant heterogeneity between individual immune responses. The clinical spectrum of disease may partly be the result of individual diversity in the CD4+ helper T-cell response to antigens.[12]

In contrast, allergic rhinitis or allergic rhinosinusitis is clinically defined as a symptomatic disorder of the nose, induced after allergen exposure by an IgE-mediated inflammation of the nasal membranes. It is extremely common, affecting 10-25 per cent of the population worldwide. It is not always a severe disease, but affects work productivity, social life and school performance. There are significant costs that are incurred by the condition.

Nasal polyps represent the 'ballooning' of inflamed mucosa at discrete areas within the nose. They commonly arise from the lateral nasal wall and middle meatus and are present in up to four per cent of the population.[13] The mechanisms as to why the mucosa degenerates into polyps in some individuals and not others are unknown. Much research has speculated that individual variations in epithelial structure, inflammatory mediators and immune responses account for the development of polyps.[14-16] Patients with asthma have a seven per cent to 15 per cent prevalence of polyps and may represent a group with a predisposition to a strong pan-respiratory inflammatory

response.[17] Nasal polyps are considered to represent a form of chronic focal inflammatory change and are defined as a sub-group within CRS. Although not all CRS patients will have polyps, all polyp patients have CRS even if the symptomatology is very mild. Separating CRS patients based on the presence of polyps has previously been popular but does not reflect different aetiological events.[18,19] However, the management of a CRS patient with nasal polyps is often more aggressive and may be reflective of a more exuberant inflammatory/immune response in that individual.[1]

Diagnosis and evaluation

Many symptoms have been attributed to CRS (**Table 1**). Chronic mucosal oedema and inflammatory exudate often accompany the inflammatory changes that define CRS. Thus obstruction and discharge are common symptoms of CRS. The symptoms of facial pain, pressure or headache along with reduction or loss of smell are considered less consistent. Together, these complaints of discharge, obstruction, pain and loss of smell, constitute the four major symptoms of CRS. Questions on allergic symptoms (i.e sneezing, watery rhinorrhea, nasal itching and itchy, watery eyes) while not diagnostic for CRS, identify concurrent pathological processes. Nasal symptoms may be secondary to CRS, but the physician must keep in mind the differential diagnoses especially cystic fibrosis, immunodeficiency syndromes, congenital mucociliary disorders, sinus fungal disease, neoplasia and cocaine abuse.

CRS can present with significant variability in symptom pattern and intensity. The course of CRS is often characterised by fluctuating symptoms and acute exacerbations. This can mimic intermittent allergic rhinitis. Patient presentations that are dominated by pain or headache, without corresponding nasal obstruction or discharge of similar significance, rarely lead to a diagnosis of CRS as the underlying cause of the presenting complaint. This is true even if there is supporting CT or endoscopic findings of mucosal thickening. Chronic mucosal inflammation is not a classical generator of significant pain.

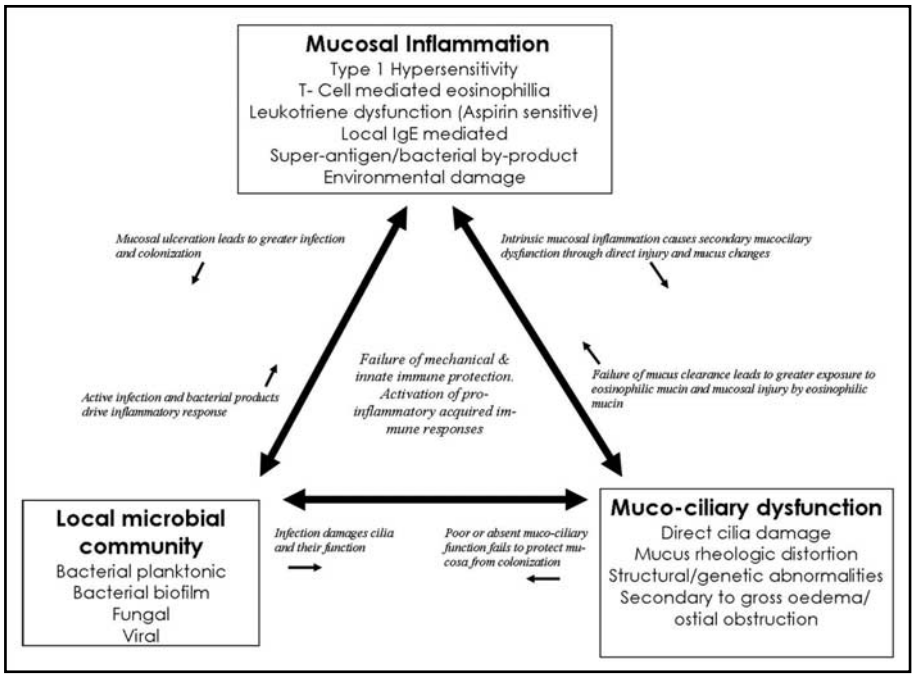

Figure 1: *Multifactorial pathogenesis of chronic rhinosinusitis.*

Local	Regional	Systemic
Nasal obstruction/congestion	Sore throat	Fatigue
Nasal discharge (anterior or posterior)	Dysphonia	Malaise
Facial pain	Cough	Fever
Facial fullness	Hallitosis	Anorhexia
Headache	Bronchospasm	
Smell dysfunction	Ear fullness/pain	
Anosmia	Eustachean tube dysfunction	
	Dental pain	

Table 1: *Local and regional systemic symptoms of sino-nasal disease*

CT scans provide an excellent assessment for mucosal thickening but provide little insight in to the nature of the histopathology (**Figure 2a, 2b**). CT scans are a highly sensitive test (94 per cent) for CRS but the specificity remains low at 41 per cent.[22] The positive predictive value of symptoms alone, as a diagnostic tool for CRS, is 73 per cent for otolaryngologists and 58 per cent for other physicians when compared to a diagnosis based on combined CT and clinical symptoms.

CT scans bear little relevance to the state or severity of CRS. Similarly, neither symptom scores or disease specific quality of life measures correlate with the distribution or degree of CT opacification.[23,24]

Visual assessment of the nasal cavity is an invaluable tool in determining underlying pathologic processes. Evaluation can be made with or without decongestion of the nasal mucosa. Assessment can be performed with rigid endoscopes or a flexible endoscope.

Mucosal oedema, polyps, discharge and crusting (**Figure 3**) form the cardinal endoscopic features of CRS. These features are not all present in allergic rhinitis patients. Positive endoscopic findings have a strong correlation with positive CT findings in CRS[25]. However among patients with chronic nasal complaints without previous sinus operations only 71 per cent of patients with negative endoscopic assessments had negative CT scans.[25] Nasal endoscopy has a 67-78 per cent negative predictive value but offers an excellent positive predictive value.[26]

Anterior rhinoscopy has little role in the diagnosis of CRS. However, it should be performed on patients examined for CRS for its simplicity and ease in which to exclude obvious septal deviation, gross polyposis or intranasal masses.

Immunological and other evaluation is appropriate in selected cases (**Table 2**).

MANAGEMENT

A. Medical

Most patients with CRS will begin with medical therapies which are variably successful. Certainly those in whom medical therapy fails are more likely to progress to surgery and medical therapy should continue post-surgery.

Broad spectrum **antibiotics** are indicated for seven to 14 days in acute infective rhinosinusitis.[27] The role of antibiotics in chronic rhinosinusitis is less clear as there are no placebo controlled studies but antibiotic therapy produces symptom improvement in 56 per cent to 95 per cent of patients with similar responses to amoxicillin/clavulinic acid, cefuroxime and ciprofloxacin. There may be a role for long term, low dose macrolide therapy presumably as an anti-inflammatory agent but further trials are needed.

Steroids, especially topically applied, have been the mainstay of medical treatment for CRS and nasal polyposis and show improvements both in symptom scores and objective measurements. In particular, shrinkage of polyp tissue size is well documented. The use of long term intranasal steroids to prevent polyp recurrence postoperatively is shown to be beneficial.[28] The brand of steroid used is not important. Nasal drops are more effective than aqueous sprays. The main side effect of intra-nasal steroids is nasal bleeding. Long term usage is considered to be safe with no evidence of tissue abnormalities seen on nasal biopsy and minimal potential for systemic side effects due to the low doses used.[29] However if inhaled steroids are used concurrently for asthma and rhinitis then there is a greater potential for systemic side effects. Contrary to traditional thinking, and more in line with asthma management, increased intranasal steroid use during acute episodes is a well established therapy.[30,31] The use of intranasally injected steroids is not recommended due to the potential for fat necrosis at the injection site or blindness.

Nasal irrigation has become increasingly popular with the use of saline, hypertonic saline and anti-fungal agents (**Figure 4**). There is general agreement that nasal irrigation improves symptoms, quality of life (QoL) and endoscopic appearances in CRS.[1,32] High volume and positive pressure delivery systems have best efficacy in access to the sinuses .[33-35] There has been recent interest in the use of topical antifungal (amphotericin B) agents in CRS[36] generated by the fungal hypothesis which postulated an altered local immune response (eosinophilia and nasal polyposis) to intranasal fungal elements, but although fungi were cultured from the majority of patients with CRS, culture rates were similarly high in normal controls. A large randomised controlled trial of amphotericin nasal lavage for three months in CRS (with and without nasal polyposis) showed no benefit over saline alone[37] and recent FDA phase three trials also showed no benefit over controls.

Aspirin desensitisation: Patients with Samters triad (nasal polyposis, asthma and aspirin sensitivity) show sustained benefit with daily aspirin therapy which has been administered orally and as intranasal lysine-aspirin.[38] Treatment

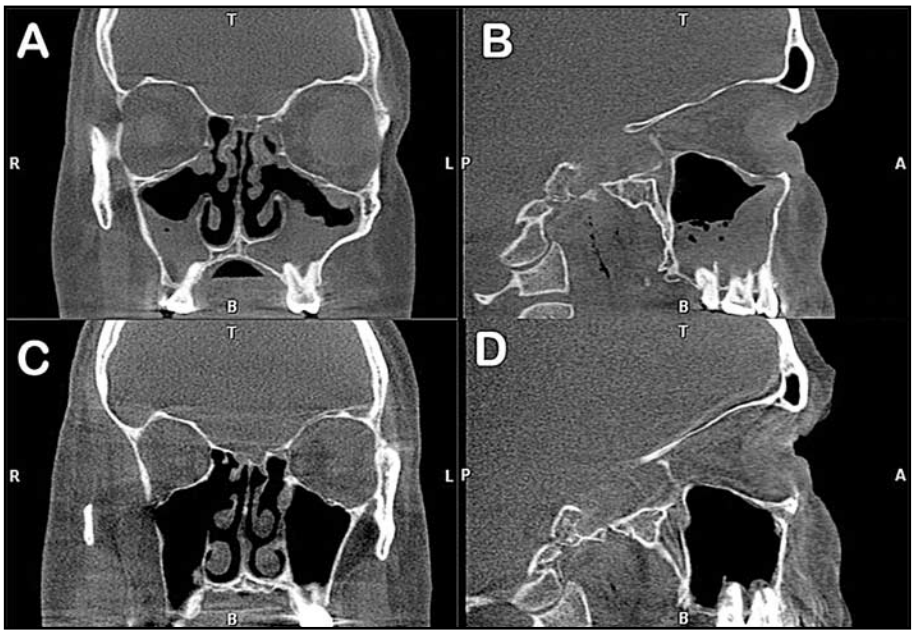

Figure 2: *Computed tomography of persistent CR despite ESS and good ventilation (2a coronal and 2b sagittal). Near complete resolution post topical therapy (2c and d).*

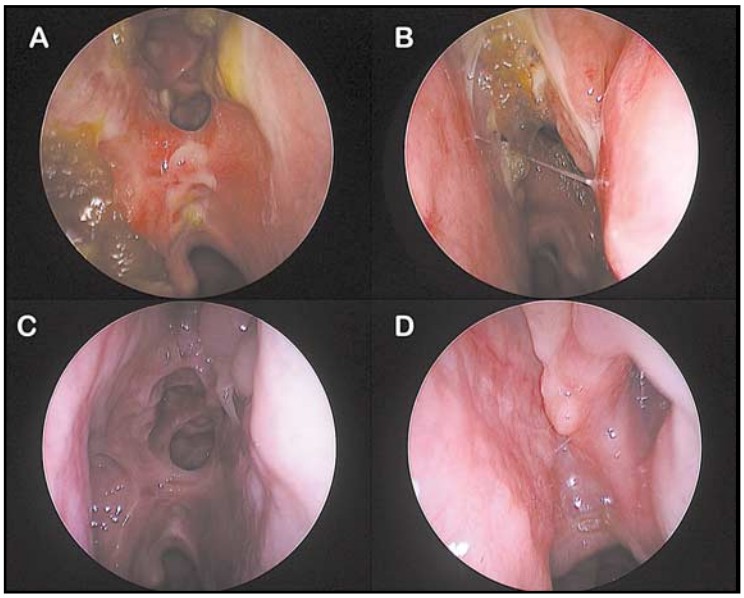

Figure 3: *The post-surgical mucosal lining before(3a,3b) and after topical therapy(3c,3d). Prominent crusting and staphylococcal and pseudomonal colonization is present (3a and b).*

results in reduced and delayed polyp recurrence. Aspirin desensitisation has also been shown to be effective in CRS with nasal polyposis and no asthma, aspirin sensitivity.

Other forms of therapy: Decongestants are frequently used by patients with acute rhinosinusitis for symptom relief but their use in CRS should be minimised due to the potential for rhinitis medicamentosa due to tachyphylaxis which occurs in about 30% of patients. Antihistamines are useful for symptom relief only and are most likely to benefit patients with concurrent allergic rhinoconjunctivitis. Anti-leukotriene agents while effective in allergic rhinitis, may produce benefits in CRS but further studies are needed. Mucolytics (eg bromhexine) may be of benefit but further studies are needed. Immunotherapy is only of benefit in CRS if there is a diagnosis of accompanying allergic rhinitis.

Mucoactive agents (Surfactants): Amphiphatic molecules possess the ability to be soluble in both water and organic solutions. They form the basis to surfactants. This effects both the solution and remaining molecular load behaviour at air-surface interfaces.[39] Pulmonary surfactant is the best known clinical example of the importance of these amphiphatic molecules. Pulmonary surfactant greatly improves the efficiency of mucocilial clearance by reducing adhesiveness of mucus to the respiratory epithelium. Acute respiratory distress of the newborn is the clinical example of the importance such agents play in respiratory function. Surfactants can have both mucoactive properties and antimicrobial properties. Chemical surfactants can interfere with microbial cell membrane permeability and cause membrane disruption. These agents are often classified as cationic, anionic or zwitterionic (possessing non-adjacent positive and negative charges) based of the charge of the hydrophilic domain present in these molecules. Cationic surfactants possess the most antimicrobial properties but are also the most irriating.[40]

There are many commercially produced surfactants. Synthetically produced detergents, soil wetting agents, paints, anti-fogging, and ski wax are all examples. The combination of PEG-80 sorbitan laurate, cocamidopropyl betaine and sodium tridecethsulfate (commonly known as Johnson & Johnson Baby Shampoo) has been shown to have both antibiofilm forming properties at 1% solution and clinical efficacy in managing refractory CRS patients.[40] Surfactants are not a treatment for aggressive polypoid mucosal change that is dominated by inflammatory Th2 response but for treating crusting, thick mucus and chronic bacterial mucosal colonization.

Citric Acid Zwitterionic Surfactant (CAZS) is currently under study for potential antimicrobial activity.[41] This agent combines the calcium bridge disrupting citric acid with the surfactant, caprylyl sulsbetaine. It was effective at reducing bacterial forming units within a sheep CRS model but not as effective as topical mupirocin.[42] There are concerns regarding possible ciliary dysfunction from any synthetic additive and future combination solutions are likely to lead to effective agents.

Immunodeficiency syndromes	IgG, IgA, IgM, IgG subsets Other specialised tests as indicated
Mucociliary dysfunction	Saccharine test, studies of mucociliary function
Cystic fibrosis	Sweat tests, genetic analysis
Recurrent infection	Bacterial culture
Autoimmune disease	ANCA (MPO, PR3)

Table 2: *Extended immunologic evaluations*

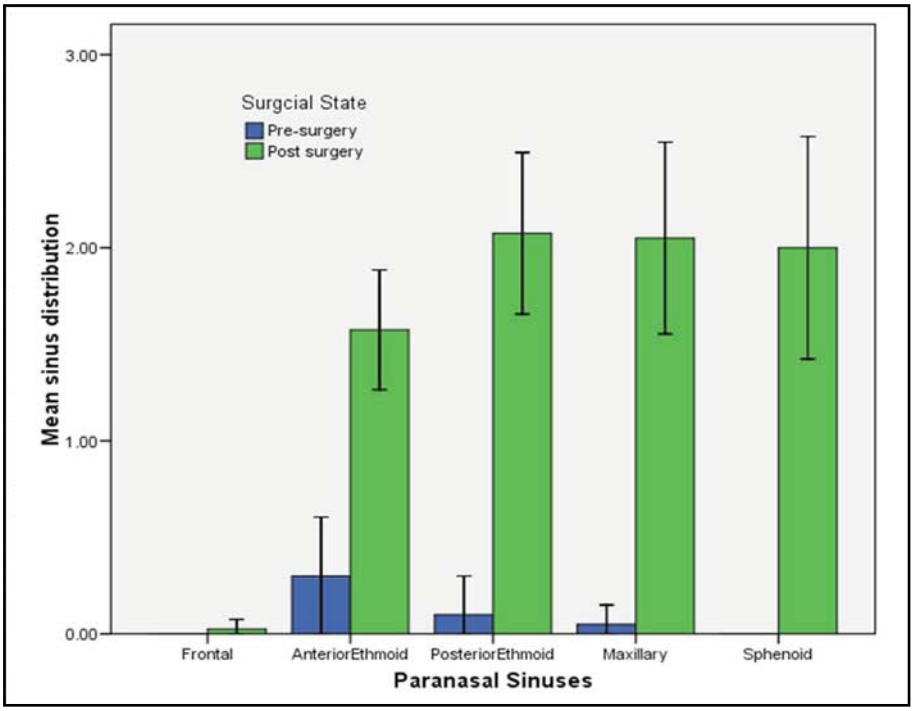

Figure 4: *High volume positive pressure nasal irrigation with retrograde flow is the most effective therapy. It will remove inflammatory mucus and antigen from the para-nasal sinuses.*

Alteration to the innate immunity: Components of the innate immune system are likely to play a significant role in the normal defense and function of sinus mucosa.[43] High concentration of salt in this air-surface liquid interface is thought to impair the activity of airway antimicrobial factors and explain some of the pathogenesis in conditions such as Cystic Fibrosis.[44] Xylitol, a non-soluble five carbon sugar, has been shown to reduce bacterial colonization in healthy controls.[44] This compound lowers ASL salt osmolaity providing enhanced innate immunity (salt sensitive) but no direct antimicrobial effect. Reduced bacterial load has been demonstrated in a rabbit model on maxillary sinusitis.[45] There is great promise for additives which enhance innate immunity, either directly or indirectly, but combinations of hypertonic salt solution and xylitol may potentially be counter-productive.

B. Surgery

If anti-inflammatory therapy and

culture-directed antibiotics over 3-6 weeks has failed, there is limited evidence that further systemic therapy will result in long-term control. The frequency of exacerbations required before surgical intervention is a subjective issue. Severity and frequency of exacerbations, intensity of treatment required for resoluton, time off work and duration of symptoms will all dictate whether and when surgical treatment is required.

Since the 1980s, endoscopic sinus surgery (ESS) has been widely employed to manage chronic rhinosinustis (CRS) refractory to medical management. There are numerous case series, prospective studies and a few randomized controlled trials to support its use.[46] Traditional surgical concepts have centred on relieving ostial obstruction and enhancing ventilation.[47] However, the role of ESS in the management of CRS has been heavily debated and scrutinized. Our knowledge-base on biofilms,[48] super-antigens[49] and eosinophilic T_h2-driven[50] inflammatory processes in CRS is rapidly expanding. Consequently, the role of ESS in the overall management of CRS has become more difficult to define. While much of the evidence for using ESS in CRS is based upon patient-centered outcomes, symptom improvement, or disease-specific quality of life measures,[46,51] little objective investigational data has been published to support the use of ESS in CRS.[52-54]

An exception exists for the distribution of topical therapies. Pre-surgery, distribution to the sinuses is extremely limited regardless of device.[34,35,55] Sprays are the least effective of all delivery devices.[34] Although multiple devices and head positions have been trialled, less than 50 per cent of most low volume applications will reach even the middle meatus.[56] In the setting of CRS with mucosal oedema it is probably only in the order of <2 per cent.[55] A fundamentally held belief amongst subspecialists treating CRS patients is that ESS improves the delivery of topical medications to the sino-nasal mucosa[57,58] yet only recent evidence exists to support this claim.[34,35] Endoscopic sinus surgery is essential to effectively allow topical distribution to the sinuses. The frontal and sphenoid sinuses receive almost no access presurgery[34] and an ostial size of 4mm+ is required to even begin seeing penetration to the maxillary sinus.[35]

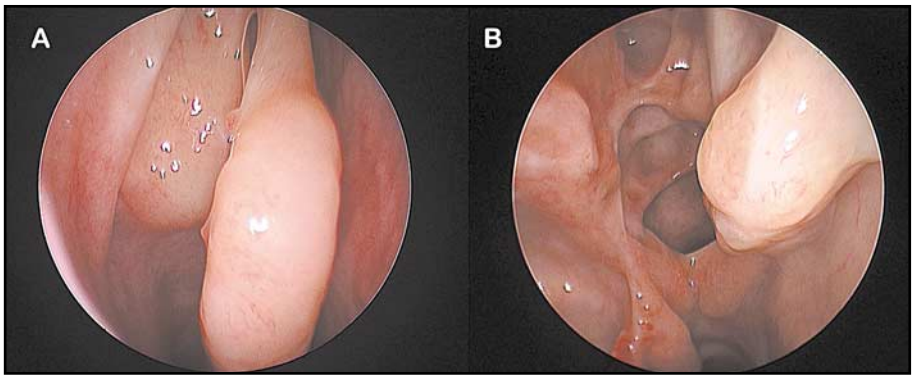

Figure 5: *The access pre(5a) and post(5b) endoscopic sinus surgery for the right paranasal sinuses.*

Modern endoscopic sinus surgery aims to be minimally invasive but maximally address the areas of concern. Careful wide exposure of the paranasal sinus system with preservation of the mucosal lining of the remaining cavity is the goal of endoscopic sinus surgery **(Figure 5)**. This allows easy management of any mucosal-based disease. Delivery of topical therapies **(Figures 2 & 3)**, the ability to perform saline sinus irrigation, improved mucocilary function and removal of obstructive polypoid tissue allows many chronic refractory conditions to be easily managed. Small limited openings in the paranasal sinuses, as performed with traditional approaches, are unlikely to assist the long-term management of most inflammatory conditions. In medically managing CRS, the pre-surgery persistence of expensive and time wasting topical therapies are probably not supported. Any benefit from topical therapy, pre-surgery, may be the result of treating secondary turbinate congestion rather than the sinus mucosal inflammation.

Conclusion: CRS is a chronic and disabling disease. A combined medical and surgical approach is required. Long term maintenance therapy is often required, similar to other chronic inflammatory airway diseases such as asthma. Topical therapies after sinus surgery provides the most direct route of therapy with the least systemic absorption. The future use of mucoactive agents appears promising.

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The Sandra David Oration

Australia and the South Pacific: Responsibility starts close to home

Dr Malcolm Cook*

It was a great honour to be invited to present the 2008 Sandra David Oration, and a great surprise to boot. While I have a Dr. in front of my name, it is recognition of years of formal study in international relations, a discipline far removed from medicine. As a program director at the Lowy Institute for International Policy my job is to think about the "health" and future of Australia's foreign policy.

When I discovered the Ignatian roots of the Sisters of Charity and the Australian Sisters' long engagement with the South Pacific, I felt more at ease with my selection as orator – I taught for three years at a Jesuit university in the Philippines before emigrating to Australia – and with my chosen topic – Australia's long, deep and growing responsibilities in our region, the South Pacific. Unfortunately, political events in Fiji since I presented the Sandra David Oration have simply sharpened the concerns expressed below and the burdens these may well place on the Australian government and wider community.

The global challenge

Our mission at the Lowy Institute is to provide new insights into the complex international policy questions facing Australia and questions where Australian actions can have an appreciable effect. Addressing the first part of this challenging mission, one of the greatest international policy questions facing the world today is the awesome set of challenges facing weak and fragile states and the local and international costs involved when these challenges are not met. These challenges, of course, are most deeply felt by the populations of these weak and fragile states themselves. The travails of asylum seekers coming to Australia that are played out on television screens and newspaper front are powerful testament to this.

However, through heightened security concerns and the long-standing belief that wealthier states (usually former colonial powers) have a global responsibility to help poorer states and their populations, the problems of weak and fragile states are an increasing focus of the developed world as well. Again, the selection of international news stories and angles reflects this reality. Coverage of Afghanistan (and now Pakistan) and what Australia's contribution to this wicked problem of a failed and potentially failing state should be is a daily occurrence as are the threats to sea-borne trade in the Gulf of Aden emanating from lawless Somalia.

One of the most challenging and frustrating elements of this growing focus on weak and fragile states is that there are very few examples of effective state building or re-building in the modern era. There are many more examples of failures or at least quite incomplete successes. This dour assessment is particularly true for examples where an external power is attempting to "build" or "re-build" a foreign state. There is no handbook for state strengthening either for the weak and fragile states themselves or for interested outside powers. Unfortunately, the only seemingly universal axiom is that it will take years if not decades and progress will be hard to measure early on. This is a not a situation that fits well with regular approaches and expectations of government policy, especially in foreign and development policy.

The South Pacific challenge

The second part of the Lowy Institute's mission is to focus on policies and regions where Australian actions – government, business and civil society – can make a direct and significant impact. On the global scale Australia is only a small power – the world's 15th largest economy with the 12th largest defence budget and accounting for less than two per cent of global greenhouse gas emissions – or a "creative middle power". In the South Pacific, Australia is a veritable great power and a former coloniser. New Zealand, the only other

economically and administratively developed country in the region, is only one-seventh the size of Australia economically.

Yet, it is a challenging region to be the resident major power. The South Pacific is the most aid dependent region in the world and is one of the most geo-strategically peripheral regions populated by a large number of micro-states. The small island countries of the Pacific from Nauru to Tuvalu due to their geographical location and make-up and tiny population sizes cannot function as fully sovereign states providing through their own means the services to their populations expected of them. Moreover, the largest states in the region, Papua New Guinea and Fiji, face very different but equally deep challenges in fulfilling the expectations of a modern state. Papua New Guinea, Australia's closest neighbour, is on track to meet none of the Millennium Development Goals despite a recent period of high mineral prices. In many key areas, development outcomes are moving downwards from a low base.

Painfully, the global financial crisis is also biting hard in the South Pacific, a region so distant in so many ways from the skyscrapers of New York and London where the crisis originated. Tourism and remittances are two key economic drivers in the South Pacific, two drivers at risk from the crisis. While other developing countries are benefitting from sharply lower food and energy prices, South Pacific economies are witnessing much less of a windfall due to the high a costs of transport of these commodities to the region and its' small, uncompetitive local markets.

In global terms, the South Pacific is one of the most vulnerable regions to the seemingly mounting problems facing weak and fragile states. It is geographically isolated far from major markets. It has a preponderance of small, widely spread micro-states, often with ethnically and linguistically divided populations. It is not a surprise that the South Pacific then does perform badly in development terms compared to other regions of larger countries closer to major global markets and that many of the states are unable to provide their populations with the required public services not to say effective representation globally.

It is not a surprise that foreign charitable organisations and governments continue to play such large roles in funding and even providing many of the state basics in the region. Alas, there are few signs that this level of external dependence will wane any time soon. Rather the growing challenges of rising populations, unmet expectations and newer threats like climate change and HIV/AIDS may well aggravate this situation. We can see this recently with Australia's central role in the independence of East Timor and the post-independence efforts at building a Timorese state, a process that still has a very long and complicated way to go. We can see this with the major and very costly role Australia has played in regional attempts to rebuild the failed state of Solomon Islands – one of, if not the most expensive, per capita foreign solicited interventions ever and one where Australia is picking up most of the bill.

The Australian challenge

Looking outward from Australia, some of the greatest challenges we face where our actions will have the most if not decisive effect are closest to home in the South Pacific. This realisation is particularly challenging for Australia though for at least three reasons. Most abstractly, Australia has never fully seen itself as a South Pacific country, certainly less so than New Zealand. In the popular parlance of international relations in Australia, "our region" refers much more often to the wider Asia Pacific region (with emphasis on Asia) than the South Pacific. Geographically, we are in the South Pacific, but many of our major economic interests and diplomatic concerns start and extend well beyond.

This problem of interests and location is further aggravated by the cold hard fact that Australia is the only major power of any description in the South Pacific and the South Pacific is a region that rarely captures the sustained attention of the world's major powers. This may be changing in the case of the People's Republic of China, yet this is causing more concern than relief in Canberra and the wider Australian community. Canada and the United States, with help from many others, have had little or no success in guiding Haiti towards a sustainable political and economic system. Australia and New Zealand are much smaller than the United States and Canada but live in a region with many more weak and fragile states.

Finally, aggravated by the present crisis, Australia's enhanced commitment to the South Pacific and the greater financial and personnel resources this has required over the last decade face greater challenges. Australia has committed itself to tripling its aid budget by 2015 while concentrating more of this in "our region". Yet, Australia already has one of the most geographically concentrated aid budgets in the world and the South Pacific faces serious challenges in effectively absorbing more aid.

The apparent lack of measurable and significant improvement in development outcomes in the South Pacific could well test politically Australia's enhanced commitment to the South Pacific, especially in tougher economic times where the tendency may even be to look more within and less outside. South Pacific countries that are the target of this greater commitment may also find it harder to support Australia's enhanced role in their sovereign territory, particularly if they themselves do not see significant improvements. Australia's solicited interventions into the Solomons and East Timor have already faced political backlashes in Dili and Honiara and Australia's complicated, post-colonial relationship with Papua New Guinea is fraught with political pitfalls.

This gloomy forecast is certainly not light or uplifting reading. However, it does strongly suggest that the role of organisations like the Sisters of Mercy in Australia in the South Pacific will likely become more important in the coming years and that Australia engagement with our closest neighbours will grow. There is no other choice.

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Dr John Kennedy

Macular Degeneration – The New Paradigm of Treatment

Introduction

There are four major sight threatening conditions in our community – cataract, glaucoma, diabetic retinopathy, and age-related macular degeneration (AMD). Of these, up until now AMD has had the most dismal prognosis. The purpose of this article is to bring the reader up to date on what AMD is and how it affects vision, and to explain how new and exciting forms of treatment are completely changing our management of this condition.

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What is macular degeneration?

Macular degeneration is the term given to a group of conditions causing progressive loss of central vision, leading to inability to read, recognise faces and drive. This has a significant effect on patients' independence and quality of life. The most common type is age related macular degeneration (AMD). As the name implies, age is the major risk factor. AMD is the most common cause of irreversible visual loss in the elderly in the developed world. Between 65 and 75 years of age about 10 per cent of people have some impairment of vision due to AMD, and over 75 years about 30 per cent are affected. Even in late stages people usually maintain peripheral vision and can see to walk around (often with difficulty), but it is the loss of central vision that has the most devastating effect on lifestyle. (**Figure 1**)

Macular Structure and Function

The macula is the central posterior portion of the retina. It contains the highest concentration of photoreceptors, specifically retinal cones, and is one of the most metabolically active areas of the body. The macula is responsible for central high resolution visual acuity such as for reading and any fine detail. The other retinal photoreceptors are the rods, which are more in the peripheral retina and are responsible for night vision and peripheral visual fields. The central part of the macula (fovea) contains no blood vessels but derives its oxygen and nutrient supply from the adjacent vascular layer – the choroid. Separating these two layers of the eye is a membrane called the retinal pigment epithelium (RPE) which is very important, controlling movement of nutrients and oxygen between the macula and the choroid. (**Figure 2**)

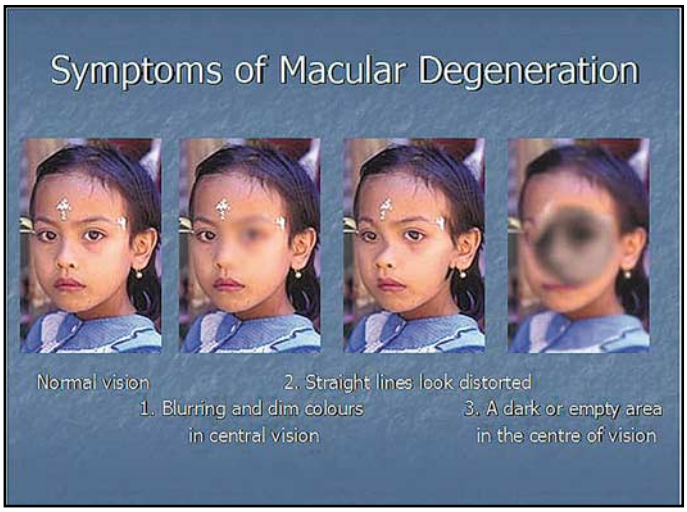


Figure 1:

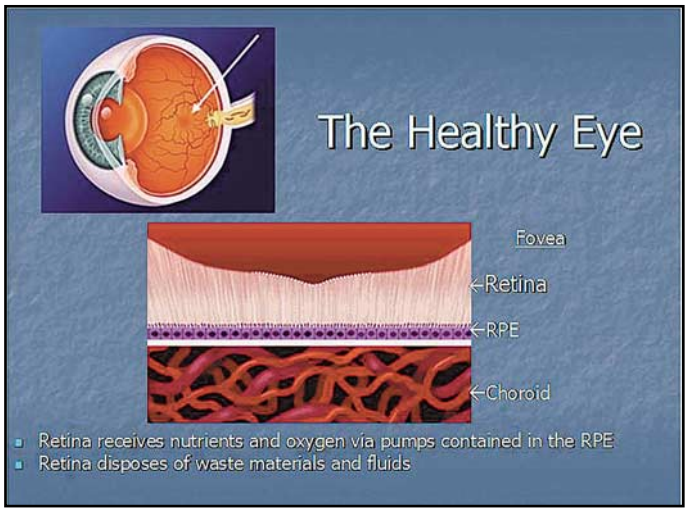


Figure 2:

AMD

AMD is an exaggeration of the normal ageing process and the early signs are usually discrete yellow spots at the macula (drusen – **Figure 3**), together with hyperpigmentation or depigmentation of the RPE. This can then progress to either of two forms:

Dry (atrophic) AMD (**Figure 4**), which is characterised by geographic atrophy of the RPE – in other words the RPE gradually wears out with age.

Wet (neovascular) AMD (**Figure 5**), the feature of which is the growth of abnormal blood vessels (choroidal neovascular membranes – CNVM) through the RPE and then these are at risk of bleeding causing a more dramatic and sudden visual loss than the gradually progressive geographic atrophy of dry AMD. The end stage of wet AMD is a formation of a sub-retinal fibroglial scar.

The two types have different characteristics : atrophic AMD is the more common, and the deterioration in vision tends to be slow and gradual. Neovascular AMD has a more sudden onset, and is more rapidly progressive and destructive.

Risk Factors

There are "uncorrectable" risk factors – advancing age, family history, genetic (more common in Caucasians, as increased melanin in the choroid is protective), and also several clear "correctable" factors – smoking (3x higher risk, dose-duration related), vascular markers (hypertension, obesity), nutritional (high dietary intake of vegetable fat, low intake of antioxidants and zinc). The effect of cataract surgery on the progression of AMD remains uncertain – while some studies point to an acceleration of AMD after cataract surgery, others show no effect.

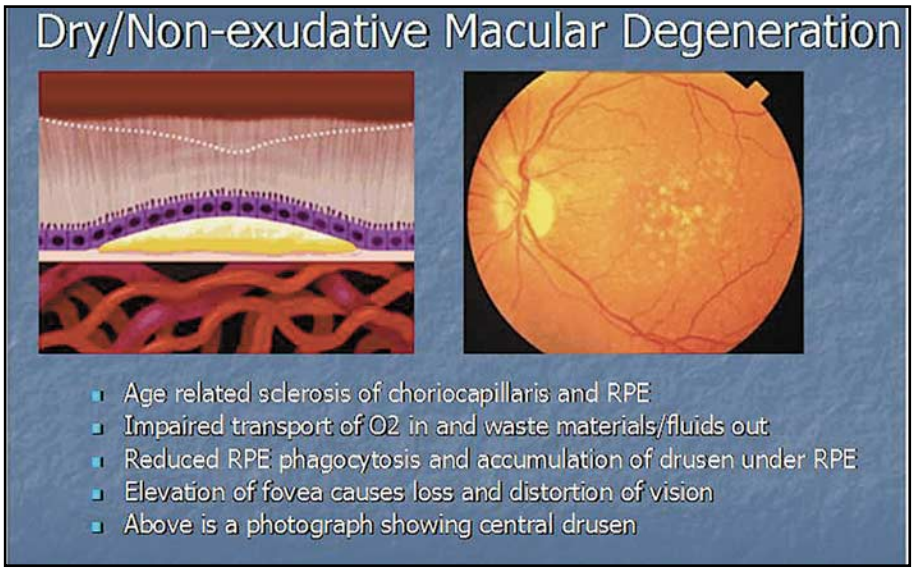


Figure 3:

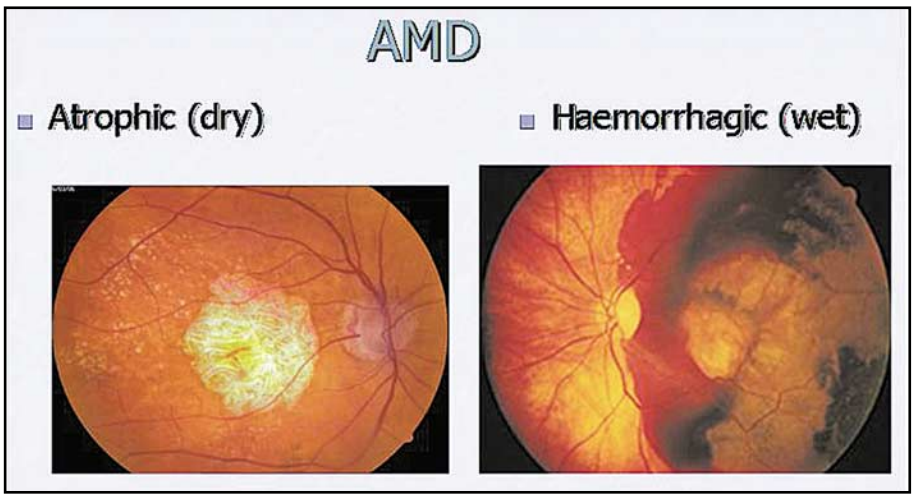


Figure 4:

Diagnosis

Diagnosis of AMD is made following a thorough retinal examination, together with retinal photography, fluorescein angiography (FA – **Figure 6**) and an optical coherence tomography (OCT – **Figure 7**) scan.

FA involves an intravenous injection of fluorescein dye and then high speed photography to examine the circulation in the retina, looking for abnormal CNVM. Fluorescein dye outlines the normal retinal vessels, and will leak out

of the abnormal vessel walls in CNVMs, with specific patterns of pooling.

OCT is new technology – an infra-red retinal scan, giving a cross sectional view of the layers of the retina, specifically looking for intraretinal fluid or fibrosis. This is a non-invasive investigation, with no injections required. The newest high definition spectral OCTs give wonderful views of each layer of the retina, allowing detailed analysis.

It is vital to differentiate the wet and dry forms of AMD, as the treatment and prognosis is different in each.

Treatment

Dry AMD

Dry AMD is the atrophic form, with a slowly progressive loss of RPE and photoreceptors in the fovea, leading to gradually progressive loss of central vision. It is essentially considered to be untreatable, but there are ways to slow down the progression:

(a) AREDS

The Age-Related Eye Disease Study (AREDS) involved 3640 patients with AMD.

AREDS found that the following combination of antioxidants and zinc may help protect against advanced AMD : vitamin C 500mg, vitamin E 400 international units, beta carotene 15mg, zinc 80mg, copper 2mg (added because high levels of zinc may cause copper deficiency). Over a 5 year period those on the AREDS formulation had a 25% reduction in the progression from intermediate to advanced AMD. There are a number of preparations available in Australia based on the AREDS formulation – "Macuvision", "Luteinvision" – and most ophthalmologists advise patients with AMD to take these daily. It may not be appropriate for all patients – one study found that beta carotene causes a 17% increase in the relative risk of lung cancer in smokers.

(b) Fenretinide

Fenretinide is an oral vitamin A protein agonist which reduces the accumulation of vitamin A toxins in the retina – by this means it is believed to slow down the progression of atrophic AMD. Fenretinide is now in Phase II studies in the US Food and Drug Administration (FDA).

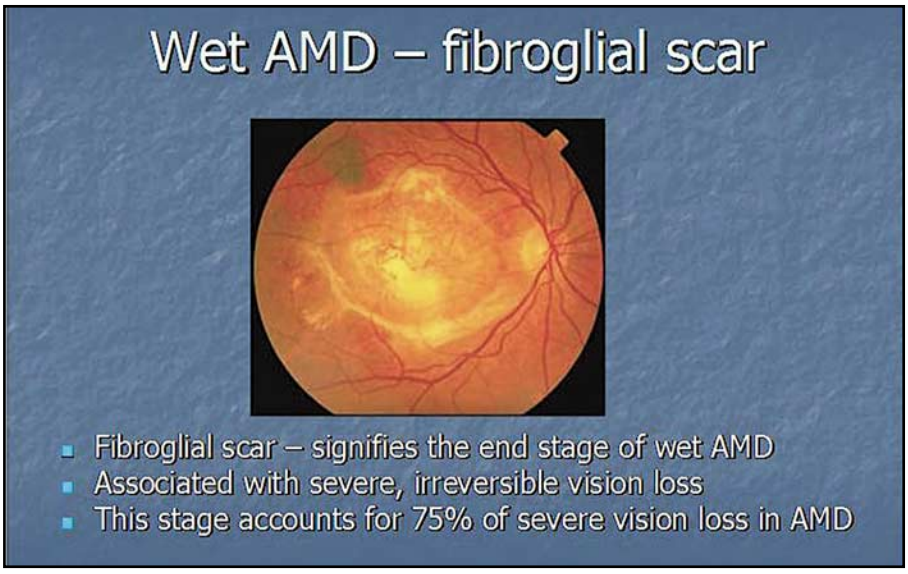


Figure 5:

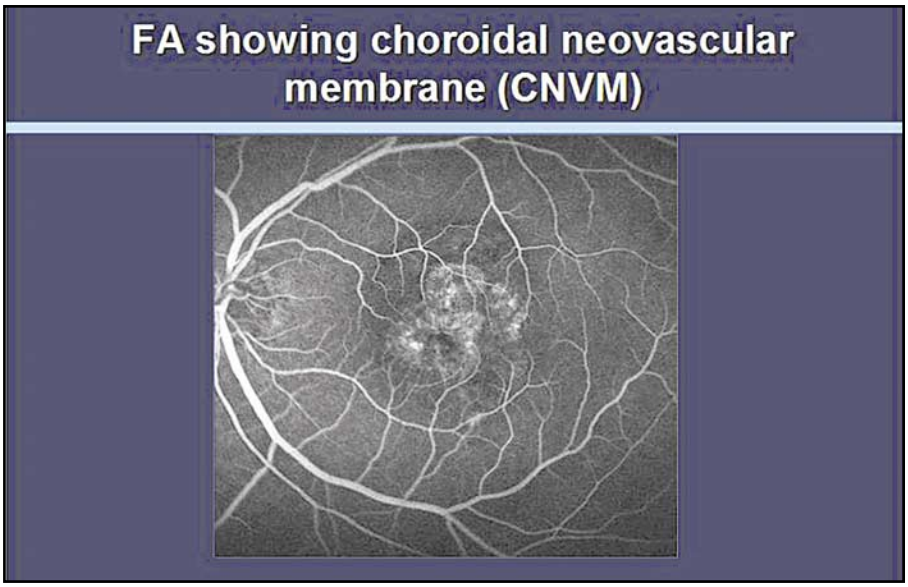


Figure 6:

(c) What to tell patients with dry AMD

Patients should be assured that the progress of the disease is slow and that peripheral vision will be maintained even if central vision is lost. Active things that the patient can do include: stopping smoking, keeping blood pressure under control, taking supplementary vitamins – Macuvision, Luteinvision. The question of dietary vegetable oils remains controversial – the most common sense advice is to cut down on canola oils and use olive oil as a margarine and in cooking.

Wet AMD

Until recently, the results of therapy for wet AMD have been disappointing. Laser and photodynamic therapy (PDT) are targeted at the individual abnormal neovascular membranes but do not address the underlying stimulus to their formation.

VEGF (vascular endothelial growth factor) – the new paradigm

The advent of anti-VEGF therapy for wet AMD has completely altered the way we approach this condition. Previously treatment was aimed at destroying the abnormal blood vessels with laser but this also destroys the surrounding retina, leaving a permanent blind spot (but still better than ongoing haemorrhage). Our aim at best was to halt the progress of the disease to stop vision from getting worse. With anti-

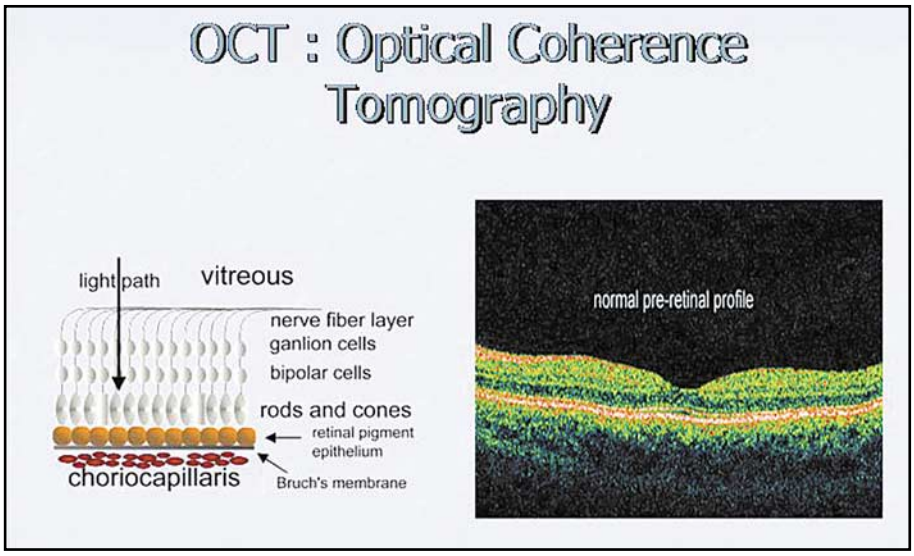
VEGF therapy, we can now aim to not only stop the progress of the AMD, but in many cases to reverse the process and improve vision. This represents a complete turnaround in our approach to wet AMD – previous therapy was at best "palliative", but now we are able to offer a "cure."

VEGF is a platelet derived growth factor involved in angiogenesis. The anti-VEGF substances are monoclonal antibodies and their derivatives which act to inhibit the growth of blood vessels. Initially used in the treatment of secondary bowel cancer, they have been found to have a beneficial effect in wet AMD by "turning off" the abnormal blood vessels. Currently, the most effective of the anti-VEGF therapies available (and now on the PBS) is Lucentis.

Lucentis inhibits the growth and leakage of the abnormal blood vessels in the retina that are the hallmark of neovascular ("wet") AMD. The active substance in Lucentis is ranibizumab, which binds selectively to a protein –vascular endothelial growth factor A (VEGF-A) present in the retina.

Lucentis is given as an intravitreal injection into the eye, under local anaesthetic, using a 30 gauge needle. Initially three injections are needed at monthly intervals, and after that according to clinical progress. The injections, done in the rooms under sterile conditions, are relatively painless – some people will have eye irritation and intermittent floaters. The most significant potential complication is an infection inside the eye – endophthalmitis – less than one in 1000. Some patients will require injections every four to six weeks indefinitely. This injection regime, together with the necessary visits for regular check ups, has implications for the ophthalmological workforce – there is a rapidly increasing number of patients needing treatment and ongoing monitoring. The numbers involved threaten to swamp medical retina clinics in the public and private sectors, and part of the new paradigm is how to most efficiently organise clinics to manage the influx of patients.

Refinement of injection schedules is aimed at minimising the number and frequency of injections required, with careful monitoring of each patient's macular thickness by OCT and visual acuity. Newer anti-VEGF agents with longer duration of action are also being evaluated – the ideal would be say a once yearly depot injection.



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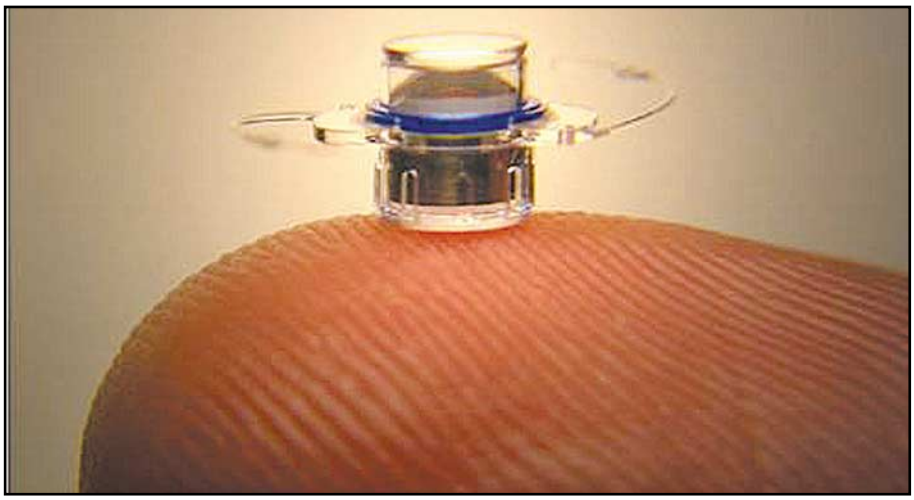

Figure 8:

FUTURE DIRECTIONS

(a) IMT(intraocular macular telescope) and other implantable devices.

When AMD has reached a point where medical therapy is no longer viable (macular atrophy in dry AMD or fibroglial scar in wet AMD) the patient is dependent on various visual aids – magnifying glass, magnifying projector, talking books etc. Another approach being developed is the surgical implantation of miniature telescopes or mirror combinations to maximise the remaining central vision. These are similar to a standard intra-ocular lens (IOL) used in cataract surgery, but specially modified to provide high magnification. **(Figure 8)**

(b) Stem cell therapy

Research at Moorfields Eye Hospital in London has shown that embryonic stem cell therapy can prevent blindness in rat and pig eyes. Clinical trials in humans are expected to begin in the next two years.

(c) Bionic eye

As part of the federal government's response to last year's 2020 summit, $50 million has been allocated to bionic eye development. There are various prototypes, using a miniature video camera worn on a pair of glasses. This sends an impulse to an array of electrodes implanted in the patient's retina, which then forms an image stimulating the occipital cortex. Initially people with severe visual loss from hereditary conditions such as retinitis pigmentosa would be trialled, but with increasing experience and refinement this technology may be applicable to AMD.

Drug-induced Long QT syndrome

Dr Jamie I. Vandenberg
Mark J. Perrin
Terry Campell
Philip W. Kuchel

Introduction

Sudden cardiac death due to cardiac arrhythmias typically occurs in patients with pre-existing heart disease. Sudden cardiac death can however also occur in patients with structurally normal hearts either as a consequence of an inherited mutation in a cardiac ion channel gene or as an unintended side-effect of many prescribed medications, i.e. drug-induced arrhythmias. The vast majority of drugs that can cause drug-induced arrhythmias and sudden death do so by inhibiting the *human ether-a-go-go* related gene (hERG) K^+ channel, a voltage-gated potassium channel that is highly expressed in the heart. Inhibition of the hERG K^+ channel by drugs results in a very similar phenotype to that seen in patients with the congenital long QT syndrome and so is often referred to as drug-induced long QT syndrome. Our group, at the Victor Chang Cardiac Research Institute, is investigating the molecular basis of drug binding to hERG K^+ channels with the aim of developing high throughput assays to screen for drugs that may have this potentially fatal pro-arrhythmic side-effect.

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Clinical Impact

The genesis of cardiac arrhythmia requires both a "substrate" that is conducive for the generation and maintenance of arrhythmia and a "trigger" that initiates the arrhythmia.[1] The most common substrate is a structural abnormality, for example, a fibrotic scar following a myocardial infarct. The substrate however can also be an inherited gene defect, as for example occurs in the congenital Long QT syndrome.[2] More disturbingly the substrate may be iatrogenic, i.e. induced by drugs that may have been prescribed for cardiac reasons or, just as often, prescribed for a wide range of non-cardiac disorders.[3] Although the incidence of drug-induced cardiac arrhythmias is rare, given that they can occur with almost all classes of drugs and can be fatal, it is important for all clinicians to be aware of them. Further, the potentially devastating consequences of drug-induced arrhythmias has resulted in much stricter regulatory guidelines being imposed on the pharmaceutical industry with respect to the need for a much more extensive assessment of the pro-arrhythmic potential for all new drugs coming to the market. In recent years considerable progress has been made in elucidating the molecular basis of drug-induced arrhythmias, however it remains very difficult to predict both at a population level and at an individual level which drugs are most likely to cause arrhythmias and when this may occur.[3]

Electrical activity of the heart

Maintenance of the normal rhythm of the heartbeat is achieved by a high-fidelity electrical communication system. The most important of the molecular building blocks of the cardiac electrical

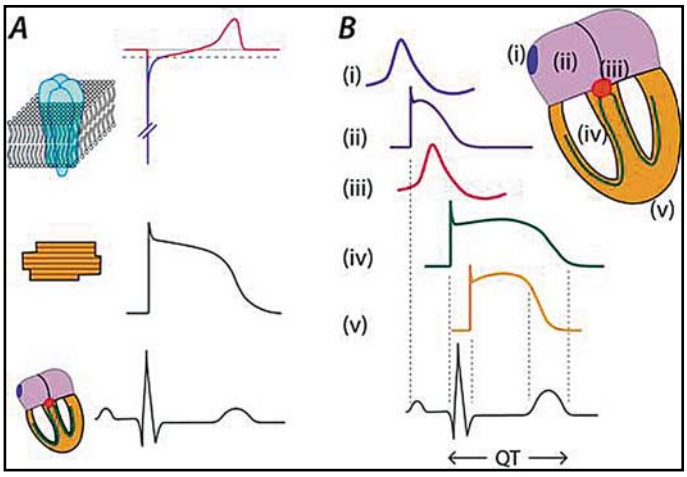

Figure 1: Electrical activity in the heart

A) Electrical activity in the heart at (i) molecular level: ion current flows through ion channels in the cell membrane, (ii) cellular level: the action potential represents the integrated activity of all the ion channels in the cell and (iii) whole heart level: the electrocardiogram represents the summed activity of all the cells in the heart. In panel (i) inward current flow is shown in blue and results in rapid depolarisation, outward current is shown in red and results in repolarization. The region between the dashed and dotted lines indicates the region of relatively low net current flow and corresponds to the plateau of the action potential.

B) Genesis of the surface electrocardiogram. Representative action potentials from (i) sino-atrial node, (ii) atrium, (iii) atrio-ventricular node, (iv) Purkinje fibre and (v) ventricle. The p-wave corresponds to atrial depolarisation, the QRS to depolarisation of the ventricles and the T-wave the terminal repolarization phase of the ventricles.

communication system are voltage-gated ion channels (**Figure 1**). Voltage-gated ion channels are critical for the genesis of electrical signals in the pacemaker region, the conduction of these signals from cell to cell as well as for excitation contraction coupling in the contractile myocytes of the atria and ventricles. At a cellular level, the cardiac action potential represents the integrated response of all the ion channels expressed in that cell. Differences in the levels and subtypes of ion channels expressed in different cells of the heart account for the different shapes of action potential recorded from different regions of the heart (**see Figure 1**). At the whole heart level, the surface electrocardiogram (ECG) represents the summed activity of the billions of cells that make up the heart.

Inherited Arrhythmia Syndromes are Caused by Mutations in Ion Channel Genes

In almost all branches of medicine, the detailed analysis of the molecular basis of pathology in rare monogenic syndromes has led to great insights into the general mechanisms of disease and to improved therapies. The best example of this was the elucidation of the molecular basis of familial hypercholesterolaemia by Goldstein and Brown; work that contributed directly to the development of statins.[4]

The commonest monogenic arrhythmia syndrome is the congenital Long QT syndrome (LQTS).[5] LQTS is characterised by prolongation of the QT interval on the surface electrocardiogram, syncope, ventricular arrhythmias, and sudden cardiac death. The age of onset can vary from intrauterine death to late adulthood. The most common presenting symptom in the proband is sudden death, which makes the disorder particularly devastating especially when the proband is a child. At post-mortem there are no cardiac structural abnormalities and the diagnosis can only be confirmed by genetic testing. Conversely, in patients who present with syncope the diagnosis can be very simple if the electrocardiogram shows the pathognomonic feature of a prolonged QT interval (>500ms is regarded as definite and the range 460-500ms is highly suggestive).

In 1991, Doug Zipes, one of the doyens of cardiac electrophysiology research, prophetically described the long QT syndromes as "a Rosetta stone for sympathetic related ventricular tachyarrhythmias".[5] In the decade and a half following the Zipes editorial, the application of molecular genetics to congenital LQTS led to the identification of at least 10 distinct genetic loci associated with LQTS, with ~95% of genotype-positive cases due to mutations in only three genes: two potassium genes, KCNQ1 (LQTS1; ~45%) and hERG (LQTS2; ~40%) and the cardiac sodium channel gene, SCN5a (LQTS3; ~10%).[6] The ten loci associated with LQTS all encode for ion channel subunits or proteins that regulate ion channel function.[7] Further, analysis of multiple other inherited arrhythmia syndromes has found that almost all of these syndromes are caused by mutations in ion channel proteins.[8] This has led to the generally accepted hypothesis that arrhythmias represent the end result of abnormal ion-channel function, whether this is caused by genetic mutations,[2] altered levels or spatial patterns of expression,[9] modulation of activity by metabolic insults such as ischaemia[10] or inappropriate drug blockade.[11]

Drug Induced Arrhythmias

Cardiac arrhythmias have long been recognised as a potential side-effect of many drugs prescribed to patients with cardiac disease (e.g. digoxin, quinidine). The problem of drug-induced arrhythmias however really came to prominence during the 1980s with the Cardiac Arrhythmia Suppression Trial (CAST).[12] The CAST study was designed to prospectively test whether Na+ channel blockers encainide or flecainide would suppress arrhythmias in patients with asymptomatic or mildly symptomatic ventricular arrhythmias after myocardial infarction. The trial however had to be stopped early when it was found that patients treated with the active drug had a higher rate of death from arrhythmia than the patients assigned to placebo. The results of the CAST study led to an increased vigilance for drug-induced arrhythmias amongst clinicians as well as regulators. Since then multiple drugs have been found to cause drug-induced arrhythmias and the vast majority cause a particular type of ventricular tachycardia called torsades de pointes that is associated with prolongation of the QT interval, exactly analogous to the congenital long QT syndrome (**Figure 2**).

Drug-Induced Long QT Syndrome

Simultaneous with the discovery that mutations in the human ether-à-go-go related gene (hERG) can cause congenital long QT syndrome, it was

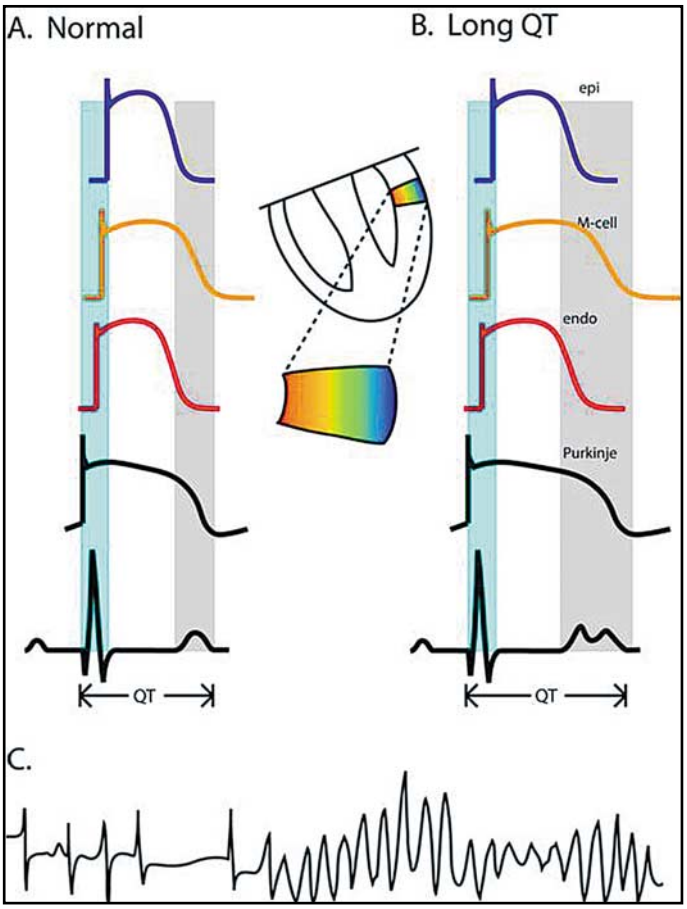

Figure 2: Cellular basis of Long QT syndrome

A) The duration of the QRS complex (highlighted in cyan) and T-wave (highlighted in grey) of the ECG reflect the heterogeneity of the timing of depolarisation and repolarization of different regions of the ventricle (colour coded according to the cartoon representation of the ventricles).

B) In long QT syndrome (congenital or drug-induced) there is prolongation of the ventricular action potential which is greater in the Purkinje fibres and mid-myocardial cells than it is in endocardial or epicardial cells. Consequently there is an increased duration of the T-wave as well as prolongation of the QT interval. In LQTS due to mutations in hERG or caused by drug block of hERG there is often a bifid T-wave.

C) ECG tracing showing onset of the typical torsades-de-pointes arrhythmia in drug-induced long QT syndrome. The voltage trace shows the typical oscillating voltage that appears to "twist" about the iso-electric line.

found that hERG was also the molecular target for the so-called Class III anti-arrhythmic drugs.[13] Class III drugs prolong the effective refractory period, by inhibiting voltage-gated K^+ channels. It was originally thought that prolonging the refractory period would be anti-arrhythmic, and under some circumstances that certainly is the case.[14] However, in structurally normal hearts, isolated prolongation of refractoriness via inhibition of hERG can induce an identical phenotype to that seen in the congenital long QT syndrome.

Many of the drugs that were first identified as causing "drug induced long QT syndrome" were drugs that were being used for the treatment of cardiac arrhythmias, e.g. quinidine[15] and sotalol[16] in patients with structural heart disease and hence high risk of arrhythmias. However, much more disturbing has been the realisation that drug block of hERG K^+ channels is not a rare occurrence, but rather occurs with a large range of both cardiac and non-cardiac drugs. These include antihistamines (e.g. terfenadine), gastrointestinal prokinetic agents (e.g. cisapride), many psychoactive agents (e.g. amitryptiline, chlorpromazine, haloperidol and thioridazine), and some antimicrobials (e.g. macrolide antibiotics, cotrimoxazole, and the antimalarial agent halofantrine).[11] The list of prescribed drugs implicated in drug-induced arrhythmias is extensive, and ever growing lists are maintained at various websites (e.g. http://www.qtdrugs.org/) Further, this risk is not just theoretical. Nine drugs, including e.g. terfenadine and astemizole have been removed from the market by the Food and Drug Administration (FDA) in the United States because the risk of lethal ventricular arrhythmias was judged to be too high relative to their therapeutic benefits and/or ready availability of alternate drugs with similar therapeutic activity but lower risk of drug-induced arrhythmias.[3]

Further, the FDA and its sister agencies around the world have recently mandated that no new drug can come to market without it first being shown that the drug does not have significant hERG blocking activity.[17] In practice, if the dose that causes 50% inhibition (IC_{50}) of hERG is less than 30x the IC_{50} for the intended target[18] then regulatory authorities require a thorough assessment of QT prolongation potential to be undertaken (see, for example, http://www.fda.gov/CBER/gdlns/iche14qtc.pdf). At a time when the number of new medical therapies reaching the market has reached an all time low,[19] testing for hERG channel toxicity represents yet another hurdle that is slowing progress in medical product development.

The story of drug-induced long QT syndrome raises a number of interesting questions. At a clinical level, the most obvious questions are: **1.** If so many drugs can block hERG K^+ channels, why did it take so long to recognise the clinical entity of drug-induced long QT syndrome? **2.** If drug induced QT prolongation is relatively common why is the incidence of drug-induced arrhythmias so uncommon? **3.** Why are some patients more susceptible to drug-induced arrhythmias? At a basic science level, the questions that have been most perplexing are: **1.** Why is the hERG K^+ channel so promiscuous with respect to drug binding? and **2.** What is the molecular basis of drug binding to hERG K^+ channels? At a translational level, given the need to screen so many chemical entities for potential hERG binding, would it be possible to develop a high throughput assay to screen for this potential harmful effect early in the drug development process? And at a regulatory level, if a potentially useful new drug inhibits hERG K^+ channel how can one assess the relative potential for life-threatening arrhythmias versus the benefits of the drug. In some instances the exercise is relatively trivial but in many others it is very complicated. One of the clearest examples of this conundrum is that of the "atypical" anti-psychotics which is discussed in an excellent editorial in the New England Journal of Medicine published earlier this year.[20]

Work at the Victor Chang Cardiac Research Institute

The rationale for the work we are carrying out in the Mark Cowley Lidwill Research Program in Cardiac Electrophysiology, at the Victor Chang Cardiac Research Institute, is that a better understanding of the molecular basis of drug binding to hERG K^+

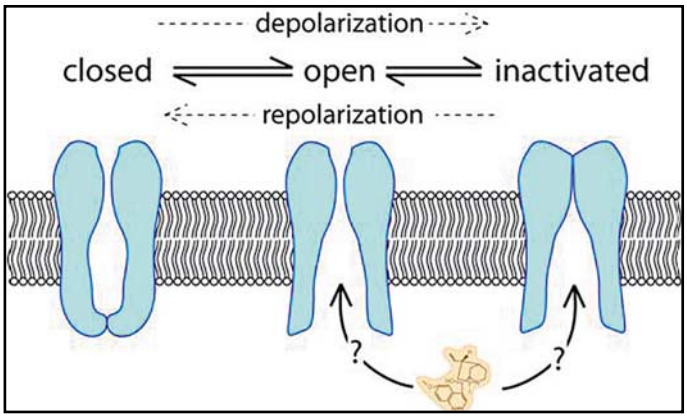

Figure 3: Drug binding to hERG K+ channels

The hERG K+ channel can exist in one of three major conformations, closed, open and inactivated states. Transitions between these three states are voltage dependent. Transitions between the closed and open states involves opening of an intracellular activation gate whereas transitions between the open and inactivated states involve opening and closing of an extracellular gate. Drug binding requires an open intracellular gate therefore in theory drugs could bind to either the open state and/or the inactivated state. Work from our laboratory has shown that binding to the inactivated state is necessary, although not sufficient, for high affinity drug binding to the hERG K+ channel.[23]

channels should permit the development of better assays for rapidly screening drugs that bind to hERG K^+ channels.

It is well established that drugs bind in the central cavity of the pore region of hERG and that channels need to open before this can occur.[21] At depolarizing potentials, hERG channels can exist in either an open or an inactivated state,[13,22] yet is has not been established whether the open or the inactivated state is preferred for drug binding (**see Figure 3**). Using a technique called 'Voltage patch clamp' in combination with site-directed mutagenesis we assayed drug binding to hERG channels that preferentially occupy the open or inactivated states. We characterized the binding of four high-affinity blockers (dofetilide, cisapride, astemizole, and terfenadine) as well as four low-affinity blockers (quinidine, perhexiline, erythromycin and dl-sotalol). All four high affinity blockers exhibited reduced affinity for the inactivation deficient mutants whereas only dl-sotalol among the low affinity blockers showed reduced affinity for these mutant channels. A kinetic model of drug binding indicated that the difference between drug binding to wild-type and mutant channels can be explained by the kinetics of drug block with the affinity for the open state being reduced 4-70 fold compared to the inactivated state depending on the particular drug studied.[23]

Our results not only demonstrate that drug binding to hERG K^+ channels is state-dependent, but for the first time allow us to calculate the relative affinities for the inactivated versus the open state, which for the drugs tested here ranged from 4-70 fold. Further, we have shown that the measured affinity for the normal (or "wild type", WT) channel, is a weighted average of the affinity for the open and inactivated states. Our results also show that preferential binding to the inactivated state is necessary although not sufficient for high affinity binding to the hERG K^+ channel.

Given the mandated need to screen all drugs for hERG binding, there has been considerable effort put into developing high-throughput screens for assaying drug binding to hERG.[3] In general, however, the results of these screens have been poor and we suggest that this is because they predominantly assay binding to the open state and therefore fail to detect many, if not all, high affinity blockers. Our data show that the difference in affinity between the open and inactivated states can be 70-fold. Therefore, it is imperative that any high-throughput screening system must assay binding to the inactivated state.

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The Role of the Schizophrenia Candidate Gene Neuregulin 1 in Schizophrenia

Dr Deepi Miller

Introduction

Schizophrenia is a chronic and disabling mental disorder that affects one per cent of the Australian population and provides a major cost to Australian society where, apart from patient and family distress, it accounts for two per cent of our health and community expenditure. Individuals who use psychoactive substances (e.g. alcohol or methamphetamine) are more likely to have mental health issues than the general population and those with a mental illness have greater mental health problems when using drugs of abuse.[1] Thus, substance use seems to be involved in the cause and course of psychotic illness but the exact nature of the relationship between psychosis and drug use is not clear.

Significantly, substance abuse contributes to the substantial social, occupational, educational and legal impairment suffered by patients with schizophrenia. Comorbid substance use disorders are associated with medication non-compliance, more severe depressive and psychotic symptoms, and poorer treatment outcomes for the mentally ill. Patients who are abusing substances are more likely to present to emergency departments with higher psychiatric acuity, have greater behavioural disturbance, and spend more time in the Psychiatric Emergency Department than the general population.

Typically, schizophrenia and substance use are studied separately. Therefore, there is a pressing need to investigate the direct impact of substances such as alcohol and methamphetamine on schizophrenia-related behaviours and how they interact with other risk factors such as a genetic predisposition to this mental disorder.

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Dopamine And Glutamate

In line with the dopamine (hyperstimulation) and glutamate (hypofunction) theories of schizophrenia, animal research has shown that dopamine agonists (i.e. methamphetamine) and antagonists for glutamatergic N-methyl-d-aspartate (NMDA) receptors [i.e. phencyclidine (PCP), ketamine or MK-801] induce a broad spectrum of schizophrenia-related behaviours such as spontaneous hyperactivity, social withdrawal, impaired sensorimotor gating, or deficits in working memory.[2-4] What has not been investigated in greater detail to date, however, is whether a genetic vulnerability to schizophrenia (e.g. mutation in the candidate gene neuregulin[1] might influence the psychotic-like potential of drugs commonly used by patients with schizophrenia and the impact this has on cognition (e.g. learning, memory) and social function.

Substance Abuse In Schizophrenia

The Australian Bureau of Statistics (National Health Survey 2006: Summary of Results 2004-05, Canberra) reported that of those patients suffering from a psychotic illness, 24 per cent had an alcohol use disorder and 16 per cent

abused amphetamines, whereas in Britain 55 per cent of people with first-episode psychosis used amphetamine and PCP over the same twelve month period.[5] In Australia, the rates of psychosis amongst methamphetamine users are 11 times that seen in the general population and one in five regular users had a psychotic episode in the past 12 months.[6] Amongst patients with a mental disorder, the lifetime prevalence of having an alcohol use disorder was 22 per cent. One in three patients suffering with alcohol abuse or dependence had an Axis I mental illness, including schizophrenia.[7] Thus, there seems to be a bi-directional relationship between drugs of abuse (i.e. targeting the dopaminergic and glutamatergic system) and alcohol on the one side and schizophrenia on the other side. A research project is currently underway at the Brain and Mind Research Institute (BMRI) to understand this bi-directional relationship.

Role Of Neuregulin 1

Genetic, functional, and morphological evidence suggest that the human gene for neuregulin 1 (NRG1) is implicated in the development of schizophrenia. An association between NRG1 and an increased risk for schizophrenia was discovered[8] and recently confirmed by a meta-analysis.[9] Within the nervous system, NRG1 is involved in key neurodevelopmental processes such as synapse formation, myelination, regulation of expression/activation of receptors (including NMDA) and neuronal migration.[10,11] All these processes are thought to be affected in schizophrenia. Importantly, NRG1 stimulation suppresses NMDA receptor activation to a greater extent in patients with schizophrenia than in healthy subjects[12] and patients with schizophrenia have altered expression level ratios of different types of NRG1 isoforms.[13] In particular, the transmembrane domain (TM) isoform of NRG1 seems to be associated with schizophrenia[14] and its animal model (i.e. *Nrg*1 TM HET mice) exhibits a well-characterized schizophrenia-related phenotype.[8,15]

Animal Models

Animal models of schizophrenia can be used to understand the pathophysiological mechanisms in schizophrenia. Highly standardised experimental strategies and few ethical limitations (i.e. in regard to drug administration regimes) represent some of the advantages animal research has over human studies. To date there are mostly single-factorial animal models of schizophrenia. These single-factorial designs cannot recreate the complexity of schizophrenia with its multi-factorial aetiology. Therefore, translational or 'bench-to-bedside' research where animals studies inform subsequent human studies are essential.

Translational Research In Schizophrenia

For this reason, a translational research project is currently underway. Stage one of this project was carried out over the past eighteen months (at the Garvan Institute) and combined genetic (i.e. *Nrg*1 mutation) and environmental factors (i.e. substance abuse) in a bi-factorial design to capture more features of schizophrenia than one-dimensional strategies. This study achieved a number of outcomes: i) established an understanding of the extent to which drugs of abuse commonly used by schizophrenia patients can elicit schizophrenia-related behaviours in an animal model of the disease; ii) showed that genetic vulnerability to schizophrenia, in the Nrg1 mutant mouse, increases the susceptibility to psychoactive effects of alcohol and drugs of abuse; and iii) confirmed the validity of the heterozygous *Nrg*1 TM mutant mouse as a potential developmental animal model of schizophrenia. The preclinical animal study (stage one) has been completed.

Stage two of this study is a translational study. It is currently underway on out patients taken from the BMRI patient population. Outcomes from the initial animal study will inform and therefore translate into the clinical patient population, providing for a more practical application of the findings. Hence this study will examine the association between genetic vulnerability and drug use patterns and their impact on cognition (learning, memory) and social function in a clinic patient population. Understanding the relationship between NRG1 and substance use in terms of cognitive and social functioning may help clinicians to better understand the role of this gene in schizophrenia.

Methods

A naturalistic clinical sample of patients, who are help-seeking, will be invited by clinicians who are affiliated with the BMRI to partake in this study. Sixty outpatients between the ages of 16 and 30 yrs with first episode or early onset psychosis, currently treated with any antipsychotic except clozapine, will be enrolled. Patients will be part of a broader Youth Mental Health (YMH) research program undertaken at the BMRI. As an adjunct to the YMH program the patients will receive a comprehensive psychiatric assessment (including a full drug and alcohol history) and have bloods taken at the commencement of the project to test for *Nrg*1 susceptibility. The study will include a record of demographics; age of onset & the nature of the patients' mental health symptoms; history of other specific mental health problems (e.g. ADHD, Conduct Disorder); past & current treatment; medical & family history. Each patient will then undergo a baseline structured neuropsychological assessment using standardised neuropsychological tests to assess their cognitive function. Many of these tests will be used to translate the findings in the animal model used in stage one of this study.

Data will then be examined to determine whether there is an association between using drugs of abuse, having the at-risk haplotype of NRG1, and experiencing greater cognitive and social impairment. The most robust at-risk NRG1 haplotype first reported by Stefanson et. al. is defined by a minimal haplotype of one SNP (SNP8NRG221533) and two microsatellites (478B14-848 and 420M9-1395).[8] One study which included 64 patients demonstrated a preliminary association between this at-risk haplotype and a delayed event-

related potential (the P300) which the authors proposed to be an endophenotype for schizophrenia.[16] Hence, for reasons of comparison, this study aims to collect data on a similar patient sample size, to investigate preliminary associations between the at-risk haplotype of NRG1 and cognitive endophenotypes. Blood samples will be collected for analysis of a number of genetic markers including NRG1.

Anticipated Outcomes

This will be the first study to specifically examine the association between genetic vulnerability to schizophrenia and a history of methamphetamine or alcohol use in a clinical sample of psychotic individuals. This research will examine whether the severity of cognitive impairment and social dysfunction in psychotic individuals with a substance use history is exacerbated by genetic risk. The outcomes from this study will help identify predictive genetic, cognitive and social markers which may help targeted interventions in at-risk individuals.

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