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Editorial

Articles

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EDITORIAL

Dr John O'Neill MD, FRACP

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Editor, Proceedings

St Vincent's has always been a leader in the advancement of cardiac surgery. The first article in this 23rd issue of Proceedings, by Dr Paul Jansz (Cardiothoracic Surgeon), describes application of the relatively new technologies of Ventricular Assist Devices and the Total Artificial Heart in the support of patients awaiting cardiac transplantation for end stage heart failure. Currently at St Vincent's, 30% of patients waiting transplantation are supported by these devices.

Professor Bruce Brew, Neurologist, is frequently a recipient of grants from the Clinic Foundation for his research using Adult Stem Cells to better understand disease mechanisms in a broad range of neurodegenerative diseases involving the brain, including the various forms of dementia. In his article on "Alzheimer's Dementia in 2011", he gives a scholarly report on the current scientific thinking with respect to this disease which is becoming ever more prevalent with our aging population.

Being myself a life-long swimmer and surfer (and a victim of exostotic occlusion of the ear canals), I found the paper on "Exostoses of the Ear" by Doctors Phillip Chang and Jaymi Dumper (ENT Surgeons) most interesting with the surgical techniques and hazards of surgery being clearly described and depicted. It should be emphasised that without appropriate protections, 50% of individuals will develop significant external auditory canal exostoses after 20 years of regular surfing.

Surgical decompression of a symptomatic nerve root is a rapid and effective treatment of the pain and potential disability associated with spinal radiculopathy. Dr Mark Winder is the most recently appointed Neurosurgeon to St Vincent's Public and Private Hospitals and Clinic. In his article, he details his approach to cervical and lumbar nerve root decompression using tubular retraction systems to provide direct and minimally invasive access to the offending pathology.

The excellent and comprehensive article by Dr Anthony Chambers, Surgical Oncologist, pertaining to advances in knowledge with respect to the interesting and fortunately rare gastrointestinal neuroendocrine tumours (which may manifest in multiple ways) will be of interest to General Practitioners, Endocrinologists, Gastroenterologists, Gastrointestinal Surgeons, Oncologists, Radiologists, Nuclear Physicians and Biochemists alike.

Type 2 diabetes is increasing in prevalence in our sadly increasingly overweight population. In his article Dr Jerry Greenfield, Endocrinologist, describes two new classes of oral medication which will be effective in certain selected subgroups of Type 2 diabetic patients.

This year's Sandra David Oration is by Professor Clifford Hughes AO, CEO of the Clinical Excellence Commission. He draws historically on the inspiration of three great women, Florence Nightingale, Sandra David and Sr Bernice Elphick RSC and describes building around their personal qualities of belief, care and passion within the Clinical Excellence Commission which was inaugurated in 2004 by the NSW Government. The Commission aims to improve healthcare in NSW by making it demonstrably better and safer for patients and a more rewarding work place.

Despite continuing uncertain economic times, the St Vincent's Clinic Foundation, with the support of the newly formed Friends of St Vincent's Private Hospital (including amongst whom are some former members of the now disbanded St Vincent's Private Hospital Ladies' Committee), continues to flourish and, as shown on pages 20 and 21 of the Proceedings, was again able to provide $747,500 in research grants and awards in 2011.

Overall it can be seen that, as originally intended by its founders Sr Bernice Elphick RSC and Dr John Roarty, the Clinic strongly maintains its mission of high achievement in patient care, teaching and clinical research.

Cardiac Mechanical Assist Devices: A Review

Dr Paul Jansz

Cardiovascular disease affects over 3.4 million Australians, with 34% of all deaths attributable to pathology of this system.[1] Heart failure comprises a significant portion of this burden and, as the population ages and more patients survive myocardial infarctions, the incidence of this is only on the rise. Despite advances in the medical management of heart failure over the last couple of decades, there remains a significant morbidity and mortality associated with end stage heart failure (ESHF). In Australia, over 2700 patients die as a result of ESHF each year.[2]

For patients who are resistant to medical management, cardiac transplantation remains the therapy of choice. However, with poor organ donation rates and resulting growing waiting lists, there is high mortality in this waiting period. This has paved the way for extensive research and development in the field of mechanical assist devices, namely ventricular assist devices (VADs) and the Total Artificial Heart (TAH), as viable treatment options for this crippling condition. The basic principle of these devices is in providing mechanical assistance to the intrinsic failing pump, the heart.

History

Since the first clinical use of cardiopulmonary bypass in 1953,[3] the concept of mechanical circulatory support has been investigated. In 1966, DeBakey reported the first successful application of a ventricular assist device in the clinical setting, using a pneumatically driven diaphragm pump in a patient who could not be weaned off cardiopulmonary bypass following a double valve replacement. The patient was successfully weaned off the device after 10 days, and proceeded to be discharged home from hospital.[4] Cooley conducted the first successful TAH in 1969, in a patient who could not be weaned off bypass following repair of a left ventricular aneurysm. The device was implanted and 64 hours of support was provided till cardiac transplantation could be done.[5]

The 1970s and 1980s were a time of progress in temporary VADs as a bridge to transplantation, as well as evolution of permanent mechanical support devices. One of the major issues with these devices was their dependence on large consoles for power and control functions, confining the patient to hospital till time of transplantation. The 1990s saw progress in this area, with smaller, less cumbersome portable devices being developed.

The modern VAD era began in 1998 with the development of the Heartmate XVE (Thoratec Corporation). Over the ensuing decade, numerous companies have invested heavily in this technology and this has led to the development of various devices that are significantly smaller and more durable. The improved technology has facilitated clinical use translating to decreased mortality and improved quality of life in patients with ESHF. VAD therapy today is very much on the rise, fuelled by very promising results in their use as bridge to transplantation as well as destination therapy in this population.

Device Types

The first assist devices developed were volume displacement pumps that were pulsatile. These are known as **'first generation'** devices, **(Figure 1)** examples of which include the Novacor pulsatile VAD and Heartmate XVE (Thoratec Corporation). The pulsatile nature is through a pusher plate system, and the inflow/outflow tracts utilise porcine valves. Limitations of this generation include its large size and limited durability with the probability of device failure shown to be 35% at 2 years.[6]

The **'second generation'** of VADs provide continuous flow through the use of rotary pump technology. These have largely replaced the first generation

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devices. Through the elimination of valves and reservoir chamber, the limitations of size and durability have been improved. These devices provide axial flow, with an internal rotor that is suspended by contact bearings within the blood flow.[7] Examples of these devices include the HeartMate II (Thoratec Corporation) and the Jarvik 2000 (Jarvik Heart Inc). With these devices, the pump is inserted preperitoneally or within abdominal musculature. A percutaneous lead provides power and control.

The newest VADs, or the **'third generation'**, **(Figure 2)** are similar to second-generation devices utilising continuous axial flow systems. However they contain no ball bearings, suspended by magnetic or hydrodynamic levitation, allowing the potential for significantly improved device durability. Examples include the HVAD device (Heartware), which is the current device of choice at St Vincent's Hospital.

Device Placement

These assist devices can provide support to the left ventricle (LVAD), right ventricle (RVAD) or both ventricles (BIVAD). LVADs have their inflow cannula connected to either the left ventricle or the left atrium, and their outflow to the ascending aorta. RVADs, supporting the right ventricle, have their inflow from either the right atrium or the right ventricle, and their outflow to the pulmonary artery. The decision for LVAD/RVAD support is determined by the function of the respective ventricles and pulmonary vasculature haemodynamics. The device can be classified as intracorporeal **(Figure 3)** or extracorporeal **(Figure 4)**, depending on the location of the pump (the pump being located inside or outside the heart respectively).

Landmark Trials Involving Ventricular Assist Devices

One of the pivotal trials for the use of current mechanical assist devices in the treatment of heart failure was published in 2001. The **REMATCH trial** (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure), randomly assigned patients with ESHF (NYHA IV, ineligible for transplantation) to either receive a VAD (Heartmate XVE, Thoratec Corp) or optimal medical management. The group receiving VADs had a 48% reduction in the risk of death from any cause, a greater 1 and 2 year survival and significantly improved quality of life at 1 year post device placement. However, these devices were still associated with only 28% survival at two years and there was an increased frequency of serious adverse events in the device group, namely infection, bleeding and device malfunction.[8]

A more recent trial, published in 2009, compared the 1st generation pulsatile pumps (Heartmate XVE) with the second generation continuous flow devices (Heartmate II). ESHF patients (ineligible for transplantation) were enrolled in a 1:2 ratio to receive either a 1st or 2nd generation device. The newer, smaller and more durable second generation Heartmate II was associated with significantly improved actuarial survival at 2 years (58% vs 24%), as well as survival free of stroke and reoperation for device repair/replacement at 2 years, when compared with the first generation device.[9] The above two monumental trials, have played a large part in the use of continuous flow VADs as long term destination therapy in ESHF.

Clinical Indications

The three major long term indications for VAD therapy include bridge-to-transplantation, destination therapy and bridge-to-recovery.

Bridge to transplantation represents the most common application to date, and studies suggest that VADs improve haemodynamic status, end organ perfusion and quality of life in patients awaiting transplantation, as well as to potentially improve post-transplant outcomes.

The indication, involving the largest potential population of patients, is the use of mechanical assist device as destination therapy. With ongoing development of pump technology and with promising results in the above mentioned trials, 2nd and 3rd generation devices are providing very significant

Figure 1: *The Heartmate XVE. First generation devices were large, heavy and prone to device failure.*

Figure 2: *The HVad (Heartware). Third generation devices are small, light, easily implanted and have no moving parts in contact with each other, making them extremely durable and less prone to device failure.*

improvements in outcomes for a large subset of the ESHF patient population. In the US, **destination therapy** comprises close to 40% of VAD implants, a number that is on the rise.

Finally, **bridge to recovery** is a promising and emerging area in the use of VADs. There is evidence of cardiac remodeling after treatment with VADs, with reduction in severity or even normalisation, supporting the notion that VADs induce reverse remodeling.[10] The use of VADs for the treatment of underlying myocardial dysfunction may be possible, however this is an area of ongoing research and further work is required prior to any clinical application.

Total Artificial Heart

In the setting of end stage biventricular failure, options for mechanical circulatory support include the implantation of a Total Artificial Heart or implantation of

Figure 3: *Extracoporeal devices are still in use today, particularly for right heart failure. The pumps sit outside the body with cannulae traversing the skin to connect with the cardiac chambers.*

Figure 4: *Implantable devices like the Heartware HVad are placed entirely within the pericardium. A small drive line exits the skin and is coupled to the controller and power source.*

BIVADs. BIVADS imply the placement of two VADs, with a VAD inserted into each ventricle. While VADs are placed for support of ventricular function, TAH are designed to take over function of the patient's heart thereby requiring removal of the native heart. The TAH replaces both the left and right failing ventricles, thereby eliminating the debilitating symptoms of heart failure. The device being predominantly used around the world is the SynCardia temporary Cardiowest TAH. A landmark trial was published in 2004, where a 79% survival to transplantation was achieved in patients implanted with the Syncardia TAH.[11] This has paved the way for the introduction of these devices in many leading centres around the world **(Figure 5).**

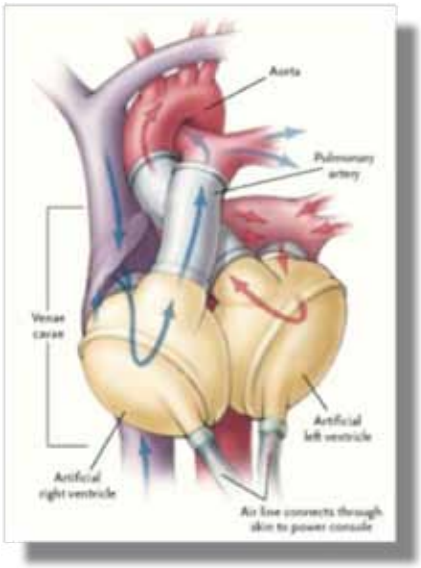

Figure 5: *Syncardia TAH. The ventricles are totally excised and replaced with the device.*

St Vincent's Experience

The St Vincent's Hospital clinical experience with mechanical circulatory support devices began in 1994. Since then, 113 mechanical assist devices have been implanted, with the use of 6 different devices over this 17-year period. St Vincent's has led the way internationally in the field and has been the lead center in international trials of new devices. St Vincent's Hospital was also the site of the first Total Artificial Heart implant in the southern hemisphere in 2010.

The majority of implants have been as bridge-to-transplantation. Currently 30% of patients awaiting cardiac transplant have a LVAD, BIVAD or TAH supporting them. Furthermore the growing body of evidence supporting its use as destination therapy will only increase the numbers of VADs and TAHs being implanted.

There has been significant improvement in the technology behind the mechanical assist devices over the last decade. This, coupled with the strong evidence of their benefit in the ESHF patient population as both destination therapy and bridge-to transplantation, makes their use an exciting area of current development. The growing population of Australian patients with ESHF will benefit greatly from this promising technology, and St Vincent's Hospital leads the way in the application of these devices in Australia.

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Alzheimer's Dementia in 2011

Professor Bruce Brew

Introduction

Recently, but most particularly in the last year, there have been very significant changes in relation to Alzheimer's dementia (AD). These range from fundamental advances in pathogenesis, diagnostic criteria, biomarkers and treatment. This update will briefly review each of these.

Pathogenesis

The pathogenesis of AD has become clearer with the recent finding that the cause of the accumulation of amyloid in the brains of patients with AD (sporadic form) is related to the impaired clearance of amyloid beta (Aβ) rather than its overproduction.[1] This has been a further boost to the validity of the most widely held understanding of AD causation, namely the amyloid cascade hypothesis. The latter essentially states that AD is caused by the brain accumulation of Aβ, usually in the form of fibrils and oligomers (Aβ1-42 being the most neurotoxic of the various forms of Aβ) that later become amyloid plaques. The competing hypothesis, namely that AD is a phenomenon primarily of abnormal tau, the protein essential for microtubule stability and cellular architecture within neurons, is becoming less likely for the following reasons. Mutations in amyloid precursor protein (APP) or the enzymes that are involved in Aβ formation have been associated with AD, albeit not the more common sporadic form. No mutations in tau have been found associated with AD. Further, animal models where there is coexpression of Aβ and tau show that Aβ oligomer formation precedes and accentuates tau-related pathology. Furthermore prevention of Aβ pathology leads to amelioration of both cognitive deficits and tau-related pathology. These observations point to the model wherein tau pathology, namely neurofibrillary tangles, is a *consequence* of Aβ aggregation.

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However, the lack of benefit of many therapies aimed at various aspects of Aβ metabolism and for that matter tau metabolism has to an extent strengthened several other hypotheses, chief among which is the vascular hypothesis. This states that vascular pathology plays an important role in AD.[2] The evidence for this is the significantly more frequent finding on brain MRI of cerebrovascular disease, manifesting as white matter hyperintensities, lacunes and brain microbleeds, in AD patients over controls. Additionally, almost all AD patients have evidence of cerebral amyloid angiopathy with approximately one quarter having brain microbleeds as a result. Nonetheless, as Cordonnier et al point out the two hypotheses are not mutually exclusive and indeed there are several lines of evidence that link the two: essentially amyloid deposition in the vessel wall and vascular disease can bidirectionally interact. Thus the amyloid cascade hypothesis is still the most likely model of AD pathogenesis. That said, there does need to be a better understanding of the hypothesis and its translation to therapy. Treatment targeted at Aβ likely needs to start at a much earlier time point, probably at the presymptomatic phase as Golde[3] points out. Further, expecting Aβ/tau therapy to improve AD maybe akin to expecting statins to reverse vascular disease. Thus there are now two directions of research for treatment driven by a better appreciation of AD pathogenesis: one looking at a much earlier stage of the disease and one examining treatment possibilities for established AD. Apropos of such therapies are the recent findings that have arisen from the International Genomics of Alzheimer's Project, a large international collaboration involving the merge of four databases for the purpose of genome screening. New mutations have been identified and new pathways relating to inflammation, lipid processing and endocytosis have been discovered. At present, it would seem that these will lead to a "refinement" of the amyloid cascade hypothesis and new targets for treatment of symptomatic AD.

The other major development in the last few years has been the demonstration

of a long presymptomatic phase. Indeed, studies using imaging and CSF analyses have shown that this phase can last 20 years or more.[4] Such a protracted presymptomatic phase has profound implications for the prevention and treatment of AD. Further, it may explain at least some of the recent negative therapeutic trial results, as treatment in the symptomatic phase is likely to be too late for complete resolution of cognitive deficits.

Diagnosis

The diagnostic criteria for AD have been revised for the first time in 27 years (http://www.alz.org/research/diagnostic_criteria/). The principal changes are that it is a positive diagnosis rather than one of exclusion and that it includes three phases: the preclinical conditions of asymptomatic at risk for AD and presymptomatic AD, mild cognitive impairment (MCI) and clinical AD with varying presentations. The preclinical conditions are to be limited to research settings at present. Mild cognitive impairment is characterized by the following core clinical criteria: change in cognition in one or more of the areas of memory, executive function, attention, language, and visuospatial skills but with only mild impact on function; independence is essentially maintained. Impairment in episodic memory (the ability to learn and retain new information) is most often associated with progression to AD. The clinical

criteria for AD are insidious progressive worsening of cognition, usually dominantly affecting memory with varying involvement of other cognitive domains such as language, visuospatial and executive functions. AD is divided into probable or possible – where there are atypical features such as sudden onset or where there are other potential explanations for dementia such as significant vascular disease. While there is an emphasis on the above mentioned positive criteria to make the diagnosis of MCI or AD, other causes of cognitive impairment still need to be considered and excluded as clinically appropriate.

The revised criteria also emphasise biomarkers to aid in the diagnosis but at this stage these are recommended chiefly for research and clinical trial purposes and "when deemed appropriate by the clinician" while more information is gathered to eventually incorporate their use into routine clinical practice at some point in the future. In essence then, biomarkers are relied on for preclinical diagnosis in research studies and in symptomatic patients biomarkers take on a more complementary role. Biomarkers are divided into amyloid related biomarkers (PIB PET scanning – a technique to demonstrate amyloid deposition in the brain – and CSF analyses for Aβ1-42) and the biomarkers of neurodegeneration (decreased fluorodeoxyglucose uptake on PET especially involving the temporoparietal cortex, atrophy on structural magnetic resonance, changes on magnetic resonance spectroscopy and CSF analyses for phosphorylated tau). There appears to be a temporal hierarchy to these with amyloid biomarkers becoming abnormal at the earlier stages of preclinical disease followed by biomarkers of neurodegeneration. While these changes are an advance, there are areas of controversy,[5,6] particularly in relation to standardization and quantitation. Nonetheless, a diagnosis of AD or mild cognitive impairment with propensity for AD would be very difficult to support if these biomarkers were negative.

Treatment

AD therapy has advanced both in terms of defining previously considered potentially effective treatments and in addressing novel therapies.[7] Cholinesterase inhibitors (donepezil, rivastigmine and galantamine) and memantine have modest efficacy in improving cognition in the short term and lead to some stabilization of behavioural abnormalities. There may be benefit in combining one of the cholinesterase inhibitors with memantine. Non steroidal anti-inflammatory drugs to counter inflammation, statins, and gingko biloba, have proven to be ineffective both in treatment and prevention. Omega-3 fatty acids, estrogens, B vitamins, folic acid, vitamin E and a Mediterranean diet all have some data suggesting potential benefit, but none is definitive. The situation with putative anti-amyloid agents is more complex but most have not been particularly potent. Further, none of these were efficacious in phase 2 trials, yet they went on to phase III trials. Enhanced removal of amyloid through passive immunization looks to be promising, while active immunization was abandoned after several deaths some years ago. Stem cell treatments to augment repair, primarily through enhancing endogenous neural stem cells, are perhaps the most appealing but they will have to be combined with an effective AD specific treatment.

Treatment for mild cognitive impairment has been disappointing. Donepezil, vitamin E, rivastigmine, galantamine and rofecoxib have not shown benefit in delaying progression to AD. These negative results may be related to the heterogeneity of mild cognitive impairment, the need for long duration studies spanning years to capture conversion to AD, and insensitive assessment tools. They are also predicated on the idea that the pathogenetic processes that are operative in AD are the same as those in mild cognitive impairment. In other words, agents that have some efficacy at the "distal" end of the amyloid cascade have efficacy at the more "proximal" part; this may not be entirely correct. The use of biomarkers in future trials may circumvent these difficulties.

Prevention

There is good evidence that reduced cognitive reserve (a concept combining the benefits of education, occupation, and mental activities), diminished physical activity, midlife obesity, alcohol intake, and smoking are associated with an increased risk of AD. Further, optimal treatment of general medical conditions such as diabetes, hypertension, and hypercholesterolaemia (the previous two factors only seem to reduce risk if treated early, that is in mid life) reduce the risk of AD.

Conclusion

Thus the field of AD research and treatment has advanced considerably in the last few years. Hopefully, strategies to prevent AD and more effective therapies for existing AD are not far off.

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Exostoses of the Ear – Their cause, classification and cure

Dr Phillip Chang

Introduction

Arising from prolonged and recurrent irritation of the bony ear canal from cold water exposure, exostoses of the external auditory canal represent the hallmark of the Australian ear. As a common clinical identity,their recognition is mandatory for all primary physicians. Their competent surgical management when occlusive is a skill that needs to be mastered by all ear surgeons.

Exostoses within the ear canal arise from years of cold wind and water exposure. This causes the bone of the ear canal to develop new bone growths that eventually constrict the ear canal **(Figure 1)**.[1] The condition is known as "surfers' ear," named after its prevalence amongst surfers in cold conditions.[2] In fact, a long term surfer (more than 20 years of regular surfing) has a 1 in 2 chance of developing significant external auditory canal exostoses,[3] and those that surf in cold water are almost 6 times as likely to have significant exostoses compared to those that only surf in warm water.[4]

This condition, however, is not limited to surfers. It can also occur with any other activity involving exposure to a cold, wet or windy environment such as white water kayaking, sailing, swimming and diving.[5] It is therefore understandable as to why exostoses are commonplace in Australian patients residing on both continental seaboards and in patients in equivalent latitudes in other countries.

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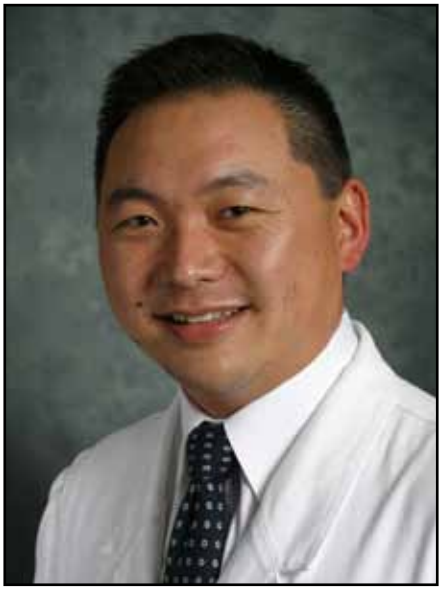
Pathogenesis

The ear canal is unique in that it represents the only part of the human body where fine vascular skin lies directly on periosteum. With cold water and wind exposure, the vasculature of this skin immediately vasoconstricts, often for prolonged periods. Once the cold water stimulus is removed, there is marked rebound vasodilatation. It is these recurrent periods of cutaneous rebound vasodilatation that are thought to provide excessive nutrition to the underlying periosteum and bone of the ear canal, resulting in the formation of bony growths or exostoses. This pathological process is often referred to as "refrigeration periostitis".[6]

Consistent with this theory, is the fact that exostoses mainly occur in certain limited latitudes, where the seasonal climate and water temperatures permit prolonged cold-water exposure. In lower latitudes the water is far too cold for any prolonged water activity and exposure. In higher latitudes the water exposure is more prolonged but the exposure is to warmer water. In real terms this equates to a much higher prevalence of exostoses in certain geographical regions, roughly 30-45 degrees both north and south of the equator.[7] This includes the eastern and western seaboards of Australia, and the coasts of South Africa, Chile, California and Japan.[2,3,8,9] Other regions, including Canada, Germany, the United Kingdom and Finland have a lower but still significant prevalence.[5,10-12]

Further evidence of the refrigeration periostitis process is the observation that exostoses are far more prevalent and prominent in the antero-inferior portion of the bony ear canal where the tympanic ring is thickest. Superiorly and posteriorly, where the tympanic ring is thinner, exostoses tend to be less frequent and more limited.

At a histopathological level, exostoses are not neoplastic and are composed of



normal laminar bone. Fagan et al demonstrated unequivocally that there was no histopathological difference between multiple exostoses and the less common solitary osteoma.[13]

Clinical Presentation

On clinical otoscopy, exostoses may appear as impressive discrete, round, ovoid, elongated excrescences or as diffuse sessile bulges of bone. They tend to occur bilaterally, though not necessarily symmetrically in their prominence.

Despite their rather obvious appearance within the ear canal, even large exostoses are often clinically asymptomatic. The significance of this condition lies in the fact that their continued growth causes a progression of symptoms.

Initially, exostoses are associated with the retention of water after swimming. This results in decreased hearing and blockage of the ear for a number of hours following water exposure. As exostoses progress further, episodes of outer ear infection (known as otitis externa or swimmer's ear) occur more frequently and can be more severe due to the entrapment

of moisture and debris. For a period of months to years this can be managed conservatively with the precaution of earplugs when swimming and the treatment of acute infections with regular microscopic aural toileting and by topical steroid-antibiotic ear drop treatment thereafter.

End-stage exostoses, with full occlusion of the ear canal, result in a painful ear with a maximal conductive hearing loss. This situation is unable to be relieved even with the aforementioned medical measures performed in an aggressive fashion. Untreated fully occlusive exostoses are a threat to the integrity of the more medial and delicate tympanic membrane and the hearing in the affected ear. For these reasons semi-urgent surgery for removal of exostoses is required. It is preferable both for the patient and surgeon that occluding exostoses be removed electively in a timely fashion before such an acute complication arises.Following surgical removal of exostoses the ear canal should be widely patent and lined with healthy, protective skin with the whole of the tympanic membrane visible on otoscopy as seen in **Figure 2a**. Most commonly exostoses are bilateral and are of similar severity as seen in **Figure 2b**. **Figure 2c** shows a coronal CT image through the external auditory canal of the temporal bone, demonstrating the extent of exostoses pre-operatively and the wide patency of the ear canal achieved with surgery.

Exostoses of various sizes also pose a problem by often preventing the full examination of the tympanic membrane and therefore contributing to the delay in the earlier diagnosis of concurrent middle ear and mastoid disease such as tympanic membrane perforations, middle ear fluid, cholesteatomata or rarely temporal bone tumours.

Anatomy Of The Tympanic Ring And Its Surrounding Structures

External auditory canal exostoses need a robust, reliable and safe technique to allow their adequate removal. The aim of surgery is to ensure no clinically significant recurrence of exostoses even with further long-term cold-water

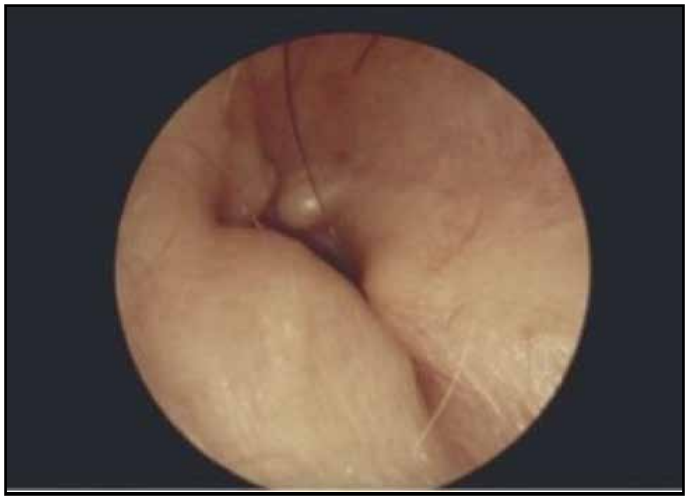


Figure 1: *Otoscopic appearance of exostoses of the left ear. Typically exostoses are multiple with the anterior exostosis being far more dominant than any posterior or superior exostosis. These exostoses are so occlusive that the tympanic membrane cannot be visualised.*

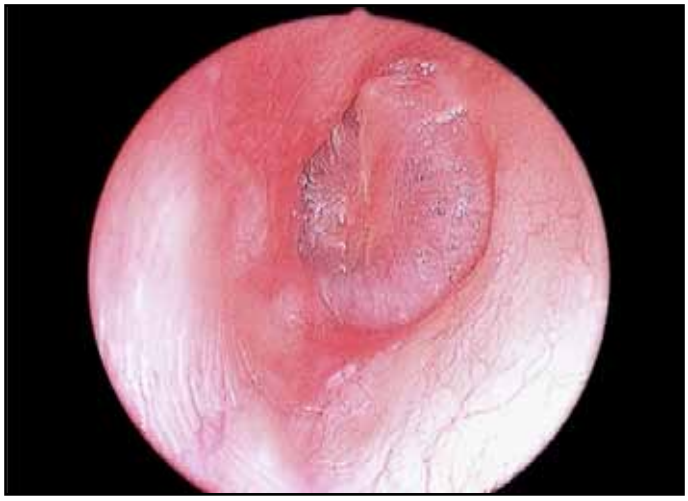


Figure 2a: *35 year old life-long dedicated surfer. The otoscopic appearance of the left ear following exostoses surgery performed 6 months earlier (a).*

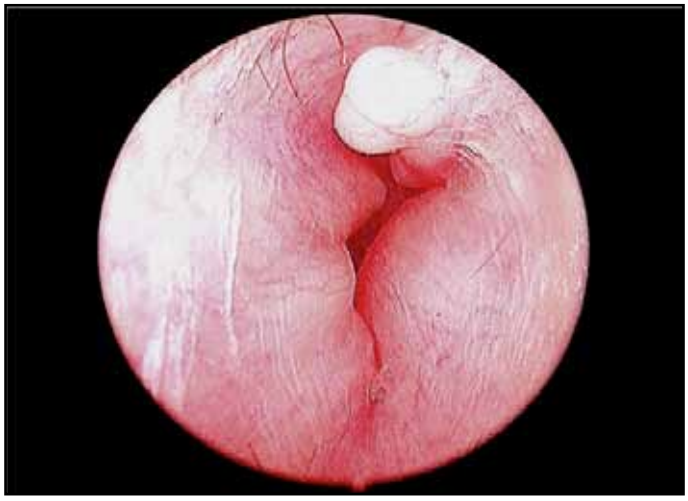


Figure 2b: *Occlusive exostoses in the right ear of the same patient now requiring elective surgery (b).*

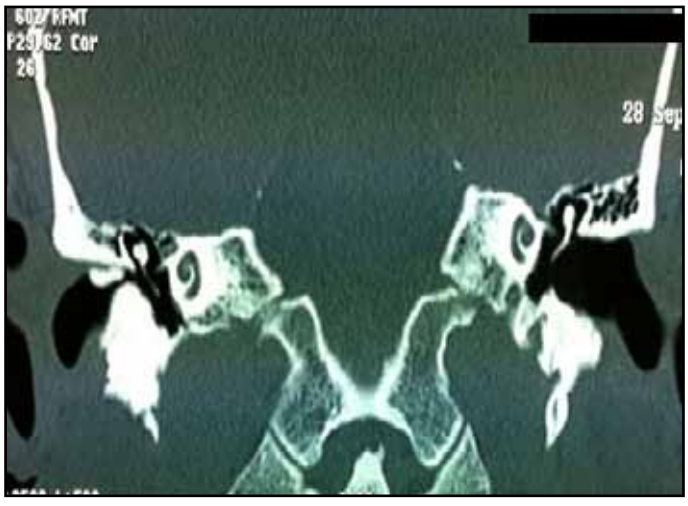


Figure 2c: *CT scan of the temporal bones (Coronal view) of the same patient. The exostoses of the left ear have been surgically removed with a cavernous bony and cartilaginous ear canal apparent. The exostoses of the right ear require semi-elective surgery, as they lie antero-inferiorly, creating a sulcus for water retention and the potential for infection against the tympanic membrane.*

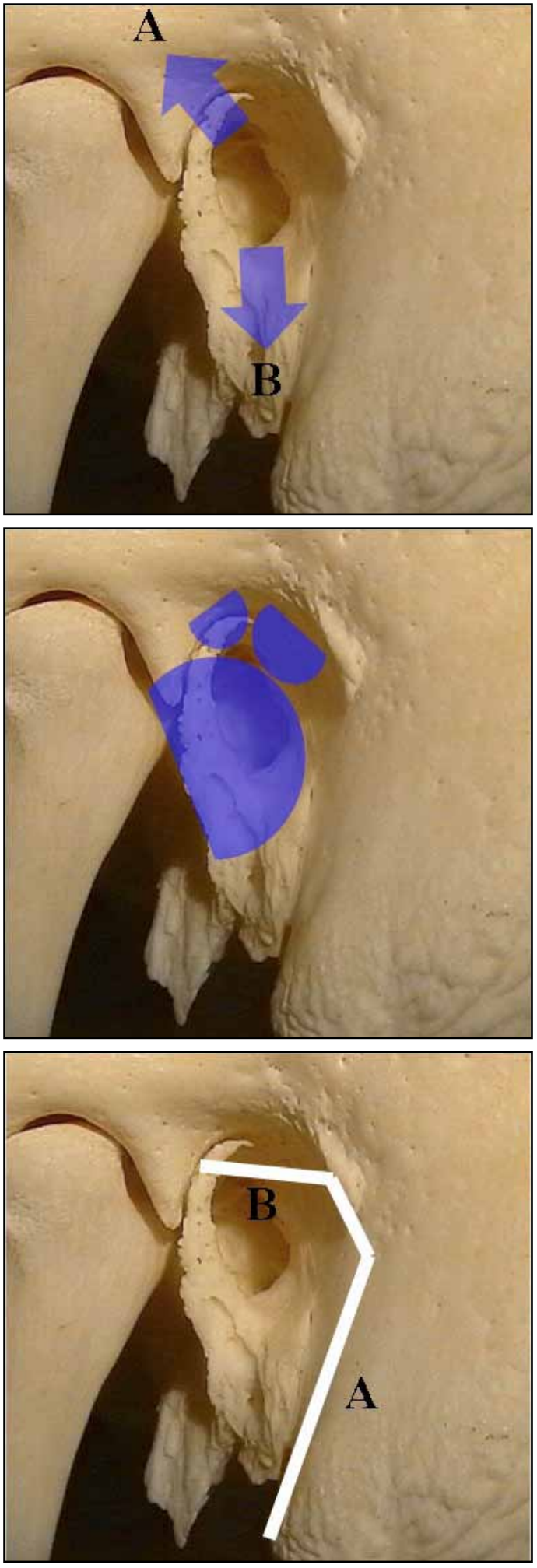
exposure. Exostoses removal therefore requires a surgical technique that needs to be both aggressive and safe **(Figure 3a)**. To ensure both these criteria are met, key points about the anatomy of tympanic bone, the facial nerve and the temporomandibular joint need to be highlighted.

The tympanic ring is thickest in its antero-inferior portion and exostoses are largest and centred on this aspect. It is exostoses in this location that leads to the greatest retention of water behind the bony growths along the floor of the ear canal. To a lesser degree exostoses occur on the posterior and superior aspect of the ear canal **(Figure 3b)**.

The facial nerve transgresses through the temporal bone in a tortuous but predictable fashion as it exits the brainstem medially and eventually emerges laterally as the five facial nerve branches, animating the superficial facial musculature. In relation to the bony ear canal, its mastoid portion can lay 1 to 2 millimetres within the bone comprising the postero-inferior wall of the ear canal. Furthermore in 70% of cases the facial nerve lies laterally to the tympanic membrane making it, at least theoretically, at risk in exostoses surgery. Less relevant and less endangered is the tympanic portion of the facial nerve that lies deep to the tympanic membrane **(Figure 3c)**. Any damage transient or permanent to the facial nerve is exceedingly rare in modern surgical series and has not been encountered within the presenting author's series to date.

The temporomandibular joint represents for the author the most vital but often the least discussed anatomical feature relevant to exostoses surgery. Not appreciated in the literature to date is the fact that the mandibular fossa makes a distinct ovoid depression apparent on the anterior wall of the tympanic ring, resulting in an ovoid prominence in the front wall of the ear canal. The fact that the exostoses of the anterior wall are the most prominent and require the most aggressive surgical removal means that this ovoid prominence needs to be surgically outlined to maximise widening of the ear canal.

Figure 3a, 3b, 3c
The left tympanic ring. Exostoses surgery requires safe but aggressive bone removal. To ensure the ear canal is 120-140% the normal physiological size at the end of surgery bone is "borrowed" from the root of the zygoma (A) and the floor of the tympanic ring (B) as shown in figure 3a. In the anatomical position, the temporomandibular joint lies anteriorly and mastoid process posteriorly. The anterior portion of the tympanic ring is thickest and widest, and therefore gives rise to the most prominent exostoses, as shown in Figure 3b. The facial nerve has an intimate relationship with the tympanic ring and the middle ear. The mastoid portion of the facial nerve (A) may lie 1 to 2 mm deep to the overlying bone. The tympanic portion of the facial nerve (B) lies in a safer position within the middle ear, deep to the tympanic membrane, as shown in Figure 3c.



The Surgical Technique

The complexity and gravity of exostoses surgery is often under-estimated by the patient and the novice surgeon. The surgery, performed under general anaesthesia, is 1.5 to 2 hours in duration and is performed as either a day surgery or an over-night procedure. Variation in duration of surgery does not reflect necessarily the size of the exostoses but rather the favourability of the surgical anatomy – as described in the authors' proposed grading system.

It is the presenting authors' preference to perform exostoses surgery with the routine use of a facial nerve integrity monitor and through a post-auricular incision **(Figure 4)**. Soft tissue dissection that includes transection and mobilisation of the skin tube lining out of the obstructed ear canal allows for complete surgical exposure of the tympanic ring.

Following surgical exposure of the tympanic ring, the occlusive exostoses themselves often prevent any visualisation of the underlying tympanic membrane or even a hint as to the direction of the true ear canal **(Figures 5a-c)**. Surgical experience is needed to "read" the configuration of the exostoses and to determine the safest direction for their surgical removal. Poor surgical orientation coupled with limited surgical experience can potentiate the creation of a bony ear canal in the wrong direction. In this suboptimal situation, this may result in the integrity of the tympanic membrane, temporomandibular joint or facial nerve being compromised.

It is necessary for any surgical technique to take advantage of the fact that the most prominent exostoses generally occur on the anterior wall of the bony ear canal. In doing so this allows for optimal orientation, access and safety when drilling more medially. Described as the "egg-shelling technique", the prominent anterior exostosis is cavitated using a selection of high-powered surgical drilling burrs. The drilling of the anterior exostosis is performed using the guidance of the ovoid prominence of the temporomandibular joint.

Mastery of the drilling of the anterior exostosis is vital. Its posterior wall serves to protect the more medial skin of the ear

Figure 4
The post-auricular incision lies just within the hair-line and has been drawn in place pre-operatively with a black marker. A minor strip of hair is shaved pre-operatively. The incision allows the soft tissue of the pinna to be reflected anteriorly to expose the whole of the tympanic ring. The facial nerve integrity monitor can be seen with fine needle leads inserted next to the eye and mouth to monitor the nerve branches to orbicularis oculi and oris during the procedure. This monitor provides another layer of safety in preserving the integrity of the facial nerve but is no substitute for good anatomical knowledge and sound surgical technique.

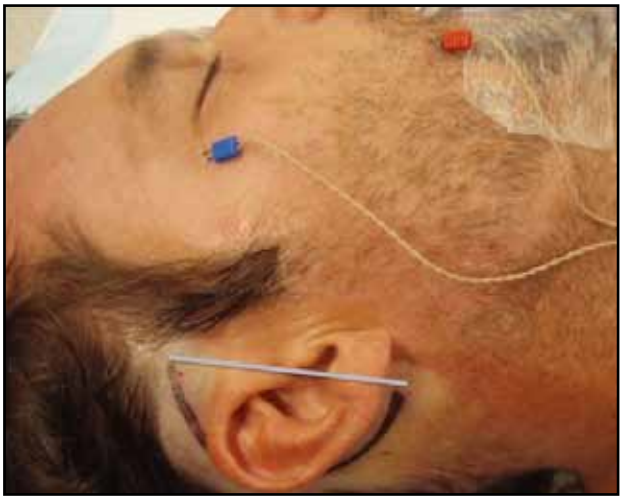


Figure 5a
Operative photos of occlusive exostoses of the right ear. With the soft tissue mobilised and before any drill excision there is no view of the tympanic membrane or the true ear canal (5a).

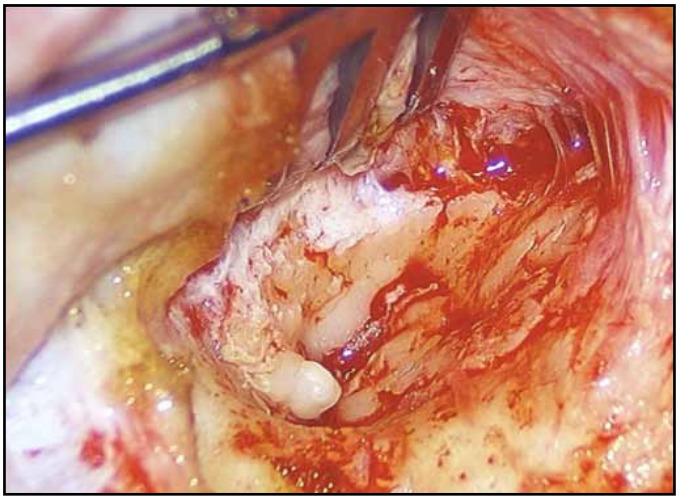


Figure 5b
Theses exostoses of the right ear being addressed with a 4 mm surgical cutting burr and a suction-irrigator providing copious cooling irrigation so as to prevent any thermal damage to the tympanic bone (5b).

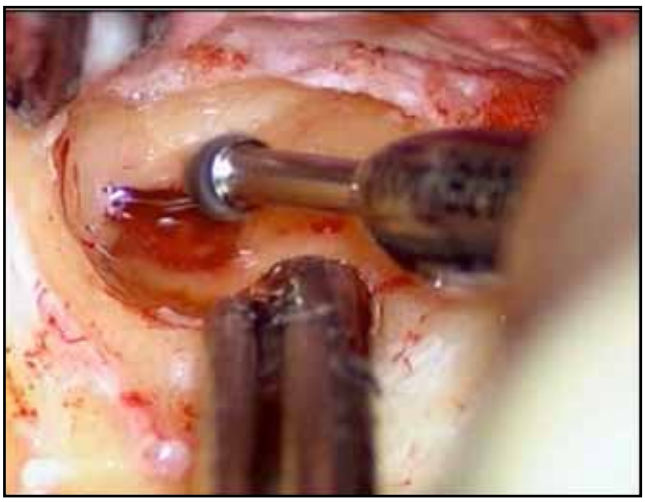
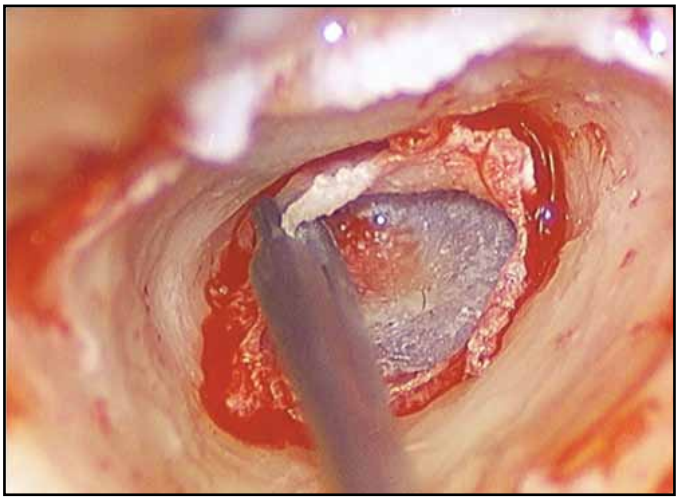


Figure 5c
The end-point of the drill dissection with the full extent of the tympanic membrane now visible (5c)



canal, vital for relining the widened ear canal. The deep wall of the cavitated exostosis protects the tympanic membrane whilst drilling. Only at the end of the drill cavitation process is the thinned wall of the exostosis removed like an egg-shell.

The removal of this egg-shell permits visualisation of the majority of the tympanic membrane. With the drum finally in view, there is greater orientation and any smaller peripheral exostoses are finally removed.

The postero-inferior exostoses which have the greatest potential to overlie the facial nerve are removed last when the tympanic membrane is visible and with maximal orientation and care.

Associated widening of the soft tissue of the cartilaginous canal and its meatus is required with a meatoplasty procedure. Antibiotic-steroid dressings are placed within the widened ear canal to facilitate healing and often require regular attendance within the 6 to 8 week healing period.

The Proposed Classification Of Exostoses

To date there has been no description in the literature of the variations in the configuration of exostoses, once they essentially occlude the ear canal. Previous reports only comment on the percentage of occlusion and do not address the prevalence of anatomic variations and their surgical implications.

Based on the surgical experience of more than 750 cases, the author proposes a new grading system that allows the classification of exostoses, determined both by their size and predominant location **(Table 1)**. This permits the ready identification of certain exostoses, the removal of which may potentially be more challenging and more hazardous, in particular to the facial nerve.

There are three grades of exostoses based on otoscopic appearance:

- **Grade 1 exostoses** are those where the anterior exostosis is the most prominent. Such an anatomical variation is the most favourable for the "egg-shelling" surgical technique, permitting the early recognition of the tympanic membrane and therefore orientation of the ear canal. In the author's experience this occurs in the great majority of cases, namely 94%.
- **Grade 2 exostoses** are known as antero-posterior exostoses. This occurs in 4% of patients. This is less surgically favourable as there is less space in the anterior exostosis for its safe cavitation by drilling. The posterior exostosis is slightly more prominent and therefore theoretically there is a very slight increase in risk to the facial nerve.
- **Grade 3 exostoses** predominantly occur posteriorly. Fortunately, these are the least common, representing about 2% of cases, experienced in the presented surgical series. These are regarded as being the least surgically favourable. Theoretically these exostoses predispose to the greatest potential for disorientation and compromise to the facial nerve, particularly in the hands of the occasional exostoses surgeon.

The Proposed Exostoses Grading System
By Chang
n=760

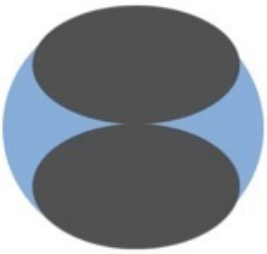
GRADE (Frequency %)	CONFIGURATION	SURGICAL RELEVANCE
Grade 1 (94%)		Most Common Most Surgically Favourable
Grade 2 (4%)		Less Common Less Surgically Favourable
Grade 3 (2%)		Rare Least Surgically Favourable

Table 1: *The New Grading System for Exostoses – proposed by the senior author*

This proposed classification is a useful tool in communicating to surgical peers about the configuration of exostoses. This classification is predictive of which particular cases of exostoses may prove to be of greater technical difficulty and more hazardous. In doing so it allows for the more high-risk exostoses, namely grade 3 exostoses, to be identified pre-operatively. The removal of such exostoses should ideally be performed with greater pre-operative work-up (including CT imaging), greater operative equipment (including the facial nerve integrity monitor) and greater caution and surgical experience.

Conclusion

Exostoses of the ear are commonplace in Australia (and other similar geographical locations) where a combination of the climate, cold water and outdoor aquatic recreational life-style conspire to promote exostoses formation. These bony growths, known to start in early teenage years, often become occlusive and mandate surgical intervention when these patients reach their third or fourth decades – if not earlier.

Any adopted surgical technique to achieve the removal of these exostoses needs to be both definitive and safe. These exostoses patients, more often than not, subject their ear canals to further decades of cold water exposure. Indeed they should be able to do so, without any clinically significant recurrence or the need for revision surgery.

The balance between aggressive surgical removal of exostoses, to deliver patients a life-long open ear canal, and safe surgery lies in a reliable, reproducible and robust technique as described in this paper. Equally a classification of exostoses is required, as proposed, which in particular is predictive of the surgical cases that may be potentially more technically challenging.

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Minimally Invasive Spinal Surgery

Dr Mark Winder

Introduction

Neurosurgical techniques, in conjunction with diagnostic neuroradiology, have evolved dramatically over the past 15 years. Specifically a paradigm shift in neurosurgical treatment of lumbar and cervical spine pathology occurred with the introduction of minimally invasive approaches, which has had a polarising effect on spinal surgeons. This paper aims to discuss the evolution, rationale and indications for minimally invasive surgery for lumbar microdiscectomies and cervical foraminotomies.

Anterior or Posterior Cervical Surgery?

The surgical management for cervical radiculopathy has been used for many decades with proven efficacy and a low incidence of complications.[1-12] The surgical procedure of choice, utilising either an anterior or posterior approach, is one of debate. It is appreciated that the anterior cervical discectomy and fusion (ACDF) results in abnormal spinal motion, placing higher shear strains on adjacent levels, increasing adjacent intra-discal pressures and leading to greater risk of adjacent level degenerative disease.[1,2,13-20] Reports of adjacent segment disease (ASD) range from 3-8% per year with a reported incidence of 25.6% at 10 years.[15,20] It remains uncertain whether this represents the natural history of cervical disc degeneration or whether it is a direct result of a longer fusion construct increasing the moment of torque at the adjacent level. Despite anterior cervical exposure being considered a relatively straightforward procedure, complications may include tracheal and esophageal penetration, vessel injury including the carotid, vertebral and internal jugular vein, neural injury of the sympathetic chain, cervical nerve roots and recurrent laryngeal nerve.[21] The incidence of vocal cord paralysis has been reported as high as 5%, with the incidence of post-operative dysphagia reported as high as 49.3%.[22,23] Although ACDF is considered by many as the gold standard there is a strong and competing belief towards preservation of normal spinal biomechanics, favouring the posterior cervical laminoforaminotomy (LF).

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Posterior Cervical Laminoforaminotomy

The LF offers an alternative treatment for cervical radiculopathy with maintenance of motion preservation. It does not require additional stabilisation or implantation of a prosthesis and as such there is minimal incidence of subsequent disease at the same segment or adjacent level.[3,17,24] It offers excellent access to lateral disc herniations and bony foraminal compromise secondary to cervical spondylosis.[6,25-29]

The initial posterior LF was devised as a midline approach, utilising a sub-periosteal lamina dissection to minimise bleeding. However, the advent of microsurgical and endoscopic techniques has now modified the access, using a paramedian incision with placement of tubular retractors. There are multiple reports with relatively large series confirming excellent results.[30,31] The advantages of the minimally invasive approaches are smaller incisions,

preservation of paraspinal muscles with minimal retraction and a direct surgical corridor to the offending region with comparable or better visualization. The approaches are complemented with shorter hospital stays (including day surgery), faster recovery times and reduced blood loss,[25,26,31-35] post-operative pain and analgesic requirements.[30,31]

Posterior approaches, despite a relatively small incision, are an uncomfortable procedure due to the bulk of the cervical spinal extensors. The advent of minimally invasive placement of tubular retractors has significantly reduced the post-operative discomfort and shortened hospital stays with no differences in clinical outcomes or associated morbidity.[8,25,26,30,32,33,35] The approach is performed as a paramidline incision approximately 18mm in length. An initial k-wire or small dilator is placed under fluoroscopy. Dilators are sequentially placed, enabling tubular retractor to be docked directly over the required lamina **(Figure 1)**. The muscles are dilated rather than stripped in subperiosteal manner as in the open procedure. Excellent visualisation is achieved using either loupes, microscope or endoscope. It is possible to perform multiple levels relatively easily with simple angulation of the retractors, or in the case of bilateral stenosis, to perform a midline incision and place the tubular retractors sequentially on each side.

Once the retractor is placed, the operation is essentially the same as for an open procedure. Hence it is not surprising that clinical outcomes are the same. The main difference is that with significantly smaller incisions and less traumatic exposures, the length of hospital stay (LOHS), operative blood loss, post-operative analgaesic requirements are less, whilst recovery is faster. Several series have reported their recovery times with 62-90% of patients being discharged from hospital the same day.[25,30-32]

The evidence for cervical laminoforamintomies as a procedure to relieve radicular pain from lateral disc protrusions is well supported with greater than 90% clinical satisfaction at long term follow up. Minimally invasive LF offers the same clinical benefits with less pain and faster recovery, maintaining its role as a safe and effective intervention.

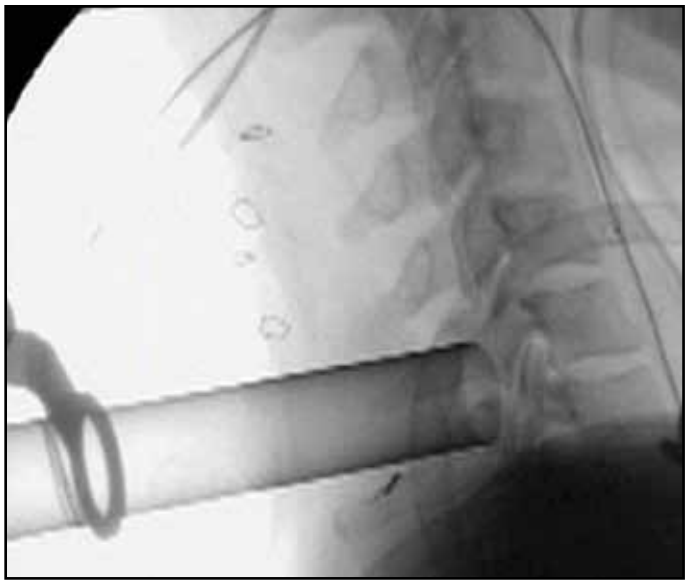

Figure 1: *Fluoroscopy showing placement of Cervical Tubular Retractors. (Medtronic MetRx®). The tube is passed through a paramedian incison and in this case docked over the C6/7 lamina and foramen.*

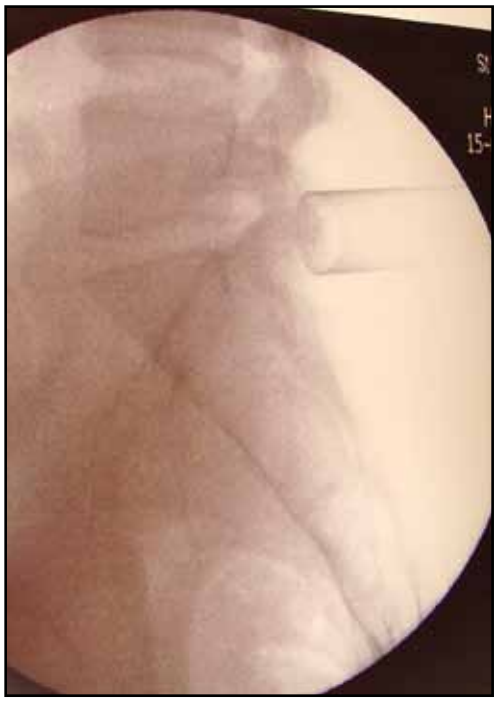

Figure 2: *Fluoroscopy showing Lumbar Tubular Retractors (Medtronic MetRx®). The tube is passed between the multifidus fibres and docked on the L5 lamina, allowing exposure of the L5/S1 disc space.*

Lumbar Microdiscectomy

Microdiscectomies have been performed as open procedures since the first report by Mixter and Barr in 1934.[36] The technique evolved from quite an extensive bony laminae and transdural approach to an extradural removal of disc.[37] Yasargil and Caspar in 1977 were credited as the first to introduce the microscope, pioneering the open, unilateral, subperisoteal, transflaval approach which represented the cornerstone of current microdiscectomy treatment.[38,39]

The concept of progressing minimally invasive surgery in the use of lumbar microdiscectomy led to a trial of percutaneous nucleotomies performed as early as 1975 with mixed results.[40] Over the next 20 years, variable techniques have been trialed including percutaneous laser disc decompression aimed at decreasing intradiscal pressure.[41-43] Disc management changed from decreasing intra-discal pressure to transforaminal decompression leading to endoscopic transforaminal discectomy systems as early as 1994.[41-45]

Foley and Smith were the first to introduce the intermuscular splitting technique for microdiscectomy in 1997, developing sequential tubular dilators allowing a direct, minimally invasive surgical corridor to the pathology.[46] Initial systems were developed such as the Medtronic MetRx®, with exponential growth of competitive systems **(Figures 2-5)**.

The purported benefits of minimally invasive tubular approaches are smaller incisions **(Figure 6)**, less muscle injury, shorter hospital stay, decreased pain and faster recovery, with equivalent clinical outcomes compared with the previous "gold standard" open microdiscectomy.

As with any new technique, there are proponents both for and against, especially in the era of evidence based medicine. Minimally Invasive Surgery (MIS) tubular discectomy is no exception generating quite dramatic polarising opinions amongst spinal surgeons, with some authors refusing to believe there is any benefit and going so far as to say it is effectively a marketing strategy. Trials are quoted stating no benefits, with others showing better outcomes. When reviewing the available data, we must be cognisant that many of the trials reported have been used to show equivalence of outcomes and in the majority of cases do not represent current practice and in most cases actual outcomes.

Arts et al has produced several papers comparing open versus MIS tubular assisted microdiscectomies.[47,48] He reported on two randomised controlled trials comparing open discectomy and MIS tubular discectomies, concluding there was no difference in LOHS, yet the hospital stays in both trials averaged over 72 hours. Post-operative institutional protocols vary significantly especially in socialised versus private medical governance. Comparing LOHS from multiple other trials, the LOHS ranges from 10.8 hrs –30 hrs.[49,50] My data concurs with LOHS averaging 15.8 hrs, which is similar in most institutions currently using MIS techniques **(Table 1)**. It is not surprising that no difference was identified by Arts et al in his series, when LOHS was three to four times as long as most other reported data for MIS discectomies.

This Dutch paper, which is quoted regularly by critics of MIS tubular discectomies, can be quite heavily criticised due in part to selection bias. Further, the quoted outcome measures use an insensitive 7-point Likert Scale, casting doubt on validity. Surgeons were supposedly experienced with the procedures, yet some had done less than 40 cases and a known learning curve exists in MIS Tubular cases.[48,50-53] Adjunctly, the incidence of durotomies was much higher than expected, likely correlating to the prolonged hospital stay and may represent inexperience with MIS cases. In essence, although some data can be taken from the paper, the results need be viewed critically, especially on reviewing the outcome measures.

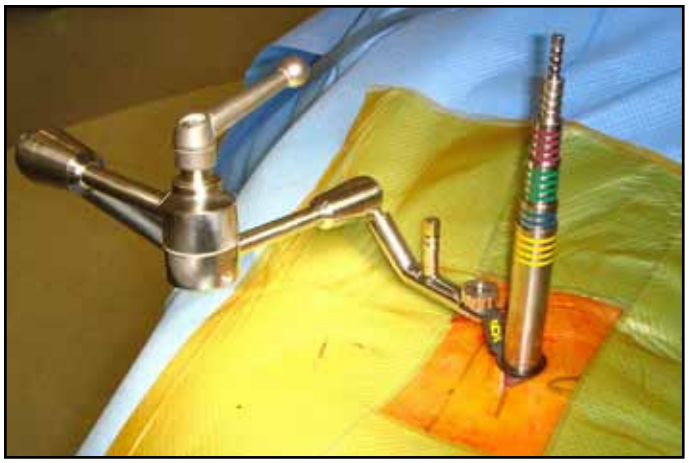

Figure 3: *Lumbar Microdiscectomy Operative Set Up. (Medtronic MetRx®). Sequential dilators with tube in place and connected with side arm.*

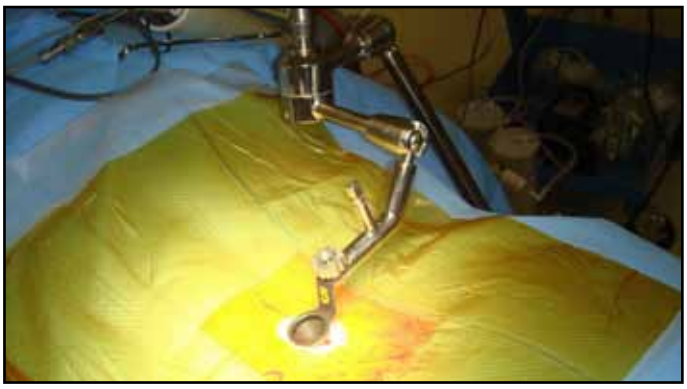

Figure 4: *Lumbar MIS Retractor (Medtronic MetRx®): Final Tubular access showing portal entry to the surgical field.*

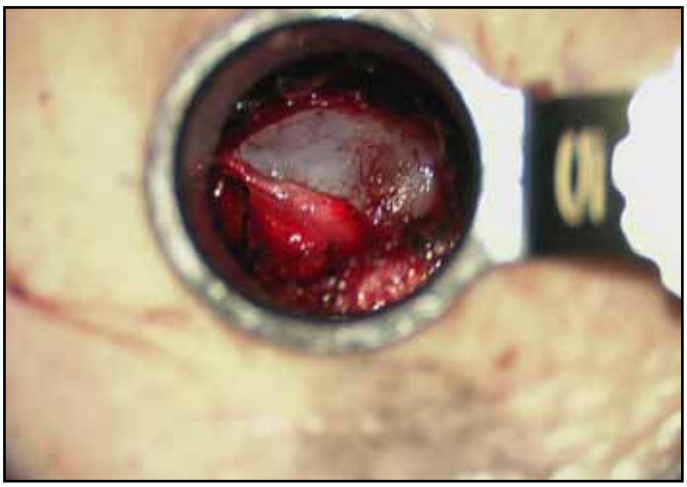

Figure 5: *Operative view through MetRx Tube: dura clearly seen allowing access to disc pathology compressing the nerve root.*

Similar results are seen when comparing analgaesic requirements and operative blood loss. There is firm data showing an earlier return to functional activity and work using MIS tubular discectomy compared to open approaches, clearly having implications on a social cost analysis perspective.[54,55]

One of the benefits of MIS tubular discectomy is the potential for less muscle injury as the multifidus muscle is dilated in a longitudinal direction rather than stripped through a subperiosteal dissection.[50,56-62] It is well known that multifidus is an extremely important lumbar spine stabiliser, with evidence that active retraining of the deep spinal rotators can aid back recovery.[63,64] Furthermore, sufferers of chronic back pain have been shown to have dysfunction

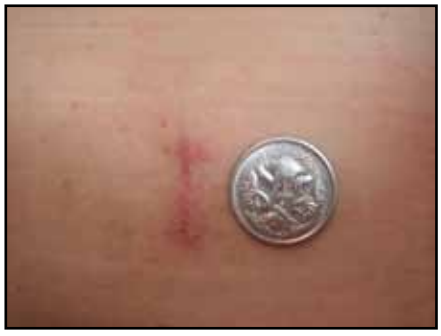

Figure 6: *Skin incision 2 weeks post-operative lumbar discectomy.*

Table 1: *Single Surgeon (MJW) Data on MIS Microdiscectomies*

Level	Numbers	Mean Age (yrs)	Operative Time (mins)	LOHS (Hrs)	Blood Loss (mls)	Post Operative Analgaesic Use (SU)	Complications (D, I, NND, R)
L5/S1	86	42.4	52	16.3	76.2	4.7	D (2), NND, R, I(1)
L4/5	34	52.8	61	21.6	104.3	6.4	NND (1)
L3/4	15	61.2	57	26.2	86.8	5.1	
Far Lateral	17	43.3	75	15.2	178.2	4.3	I (1)
Total	128	49.9	61.25	15.75	111.4	5.1	6

SU: Standardized Units for Opioid Equivalent Doses.[15,41]

Complications: D: Durotomy; I: Infection; NND: New Neurological Deficit.

Of the two infections, both were superficial, recognised at the 2-week follow up and thought to be related to sub-cuticular suture. Both treated with oral antibiotics without further complication.

The NND observed at L4/5 was due to an unusual conjoint root between L4 and L5, which led to sensory dysthaesia for 6 weeks in a partial L4 distribution. This completely resolved. The other NND in the L5/S1 groups was due to a recurrent disc causing plantarflexion weakness (4/5) 4 weeks after operation. It was re-operated and the patient made a complete recovery.

in their transversus and multifidus, with asymmetry well documented.[62-67] As such, a technique that offers a reduction in muscle injury, especially multifidus, would seem beneficial in reducing ongoing iatrogenic back pain following lumbar discectomy.

Muscle injury, essentially to multifidus, can be measured by creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) in the context of lumbar discectomy. Multiple studies have again looked at the correlation of muscle injury sustained between open and MIS discectomies with evidence that muscle injury appears greater in open procedures.[56,61,62,66,68,69] Debate exists as to the clinical significance of the sustained muscle injury, but what is clear is that open procedures generate greater levels of CPK not only in the immediate post operative period, but also taking longer to return to baseline values.[56,61,62,68] Clinically this appears to correlate with patient results of reduced post-operative pain and subsequent LOHS, all of which ultimately have a strong cost efficacy benefit.

Conclusion

Essentially, MIS tubular discectomy has shown equivalence in clinical outcomes to open procedures, without an increase in morbidity. The equivalent outcomes are expected given that the operative view, using either microscope or endoscope, is excellent and can be manipulated with simple adjustments of the tubular retractors. MIS discectomy is a safe and effective treatment with a growing body of evidence supporting shorter hospital stays, lower analgaesic requirements and a faster return to work. The concept of preservation of posterior lumbar stabilisers such as multifidus, is an attractive concept, especially as musculoskeletal rehabilitation has a strong clinical focus on it's retraining in order to help reduce lower back pain. It has also become recognised that minimally invasive procedures are ideally suited to obese patients, as it obviates the need for very large incisions in order to visualise the pathology, reducing the incidence of infection in a cohort that is recognised to have a significantly increased risk of morbidity. The reduction in post-operative pain enables faster mobilisation, reducing post operative complications such as chest infections and DVTs. Undoubtedly, further clinical data will offer more pertinent information, especially in terms of longer follow up, but given that MIS discectomies have now been utilised since 1997, with exponential growth worldwide, it has cemented itself as a sound surgical intervention.

Summary

The aim of most surgery is correction of pathology with the lowest possible morbidity. As our technology has advanced, there is evolving evidence that motion preservation and minimal tissue destruction are likely to be important factors in not only aiding recovery, but also in reducing iatrogenic complications. It has been suggested that perhaps minimally invasive surgery may be better termed "maximum access surgery", as it offers a direct surgical corridor to the offending pathology whilst maintaining clinical outcomes.[70] We all accept that open procedures have been refined to offer great outcomes; they are often the preferred approach and will always maintain an important role in neurosurgery. However it must be recognised that MIS has a role, but is a tool to use where appropriate. It is not the shining beacon of neurosurgery since it, like every other approach, has limitations. Effectively it has become part of the neurosurgical spinal armamentarium and its use should be assessed on an individual case basis, knowing that it can be technically challenging and a learning curve exists.

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Annual Grant – $30,000
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Travelling Fellowship – $10,000
Dr James Otton – Cardiology Department
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Multi-Disciplinary Patient Focused Research Grant – $25,000
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Gastrointestinal Neuroendocrine Tumours: Diagnosis and Management in the 21st Century

Dr Anthony Chambers

Introduction

Tumours arising from the neuroendocrine cells of the gastrointestinal tract are uncommon in comparison to their epithelial cell counterparts, with an incidence of only 2 to 4 cases per 100 000.[1] They were first described in the small intestine by Siegried Obendorfer in 1907. Realising that these tumours were malignant yet lacking the aggressive behaviour of carcinomas, he named these 'Karzinoide' or 'Carcinoma-like' tumours.[2] Although these tumours are considered rare 'orphan' neoplasms, their incidence is increasing, a fact that may be due to improvements in diagnosis with modern imaging techniques.[3]

Sites of gastrointestinal neuroendocrine tumours

Neuroendocrine cells are present throughout the gastrointestinal tract and are involved in the regulation of secretion and motility. The neuroendocrine tumours (GI NETs) arising from these cells occur most commonly in the small intestine, followed by the rectum, colon, stomach, appendix and pancreas. As the neuroendocrine cells in each of these structures have different functions and secretory products, so too does the biological behaviour of GI NETs in these locations vary widely **(Table 1)**. Whereas once GI NETs were referred to simply as 'carcinoid tumours' without regard to the site of the primary tumour, the World Health Organization introduced a classification system based on their site in 2000 to better reflect the different behaviours of GI NETs depending on their organ of origin.[4]

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Neuroendocrine tumours of the small intestine

The small intestine is the most common site of GI NETs, accounting for 42% of these tumours.[1] They arise from enterochromaffin (EC) cells within the wall of the intestine. The primary tumours tend to be small (often less than 10mm), occur most commonly in the distal ileum and are multiple in 39% of cases.[5] **(Figure 1)** Due to their small size the primary tumour itself is rarely detected on imaging studies and is rarely the cause of obstruction or other complications. In most cases, small intestine NETs only become symptomatic when they metastasize. For this reason, more than 90% of small intestine NETs have evidence of metastatic disease at the time of presentation.[6]

The most common site of metastases of small intestine NETs is to mesenteric lymph nodes, found in 80-91% of cases at the time of surgery.[6,7] These metastases can form large mass lesions in the small bowel mesentery. The release of tumour growth factors from these metastases causes fibrosis and desmoplasia around the nodal mass, leading to retraction and distortion of the mesentery and angulation of the intestine, producing chronic intestinal obstruction. The mesenteric vasculature may also be compromised by this process, producing localised ischaemia to segments of the small intestine and chronic abdominal pain. Mesenteric lymph node metastases have a characteristic appearance on CT scanning, forming a mass that may be calcified, with a 'spoke and wheel' appearance due to the surrounding desmoplastic reaction. **(Figure 2)**

Hepatic metastases are present at the time of diagnosis in 39-80% of cases of small intestine NETs. These metastases tend to be multiple and small in size (less

Table 1. *Neuroendocrine tumours of the gastrointestinal tract and their associated characteristics.*

Structure	Neuroendocrine cells	Neuroendocrine tumours	Hormones produced	Endocrinopathy
Stomach	ECL-cell	Gastric NET	Histamine	Rare – related to Histamine
Duodenum and pancreas	G-Cell	Gastrinoma	Gastrin	Zollinger Ellison Syndrome (peptic ulceration, diarrhoea)
Small intestine	Enterochromaffin cell	Small intestine NET	Serotonin	Carcinoid syndrome (diarrhoea, cutaneous flushing, bronchospasm, valvular heart disease)
Appendix	Enterochromaffin cell	Appendiceal NET	Serotonin	Carcinoid syndrome
Colon & Rectum	Enterochromaffin cell	Colon/rectum NET	Serotonin	Carcinoid syndrome

ECL, enterochomaffin cell-like; NET, neuroendocrine tumour

than 1cm), occurring with a bilobar distribution in a pattern described as 'miliary'. Due to the small size of the lesions, hepatic metastases are often not detected by CT, magnetic resonance or nuclear medicine scanning. The liver should be carefully inspected at the time of surgery in patients with small intestine NETs to look for this pattern of metastatic disease which can be easily overlooked.

Hepatic metastases from NETs are able to secrete serotonin and other hormonally active substances directly into the systemic circulation, thereby escaping the first-pass metabolism of serotonin that occurs in the liver. Chronically elevated levels of serotonin and other hormones from NET hepatic metastases cause symptoms of the carcinoid syndrome, characterised by cutaneous flushing, watery diarrhoea, bronchospasm and valvular heart disease of the right heart chambers. There is also recent evidence that patients with carcinoid syndrome may have symptoms and signs of reduced cognitive function.[8] Carcinoid syndrome generally only occurs in the presence of hepatic metastatic disease and patients with symptoms or signs of carcinoid syndrome should be assumed to have hepatic metastases until proven otherwise.[9]

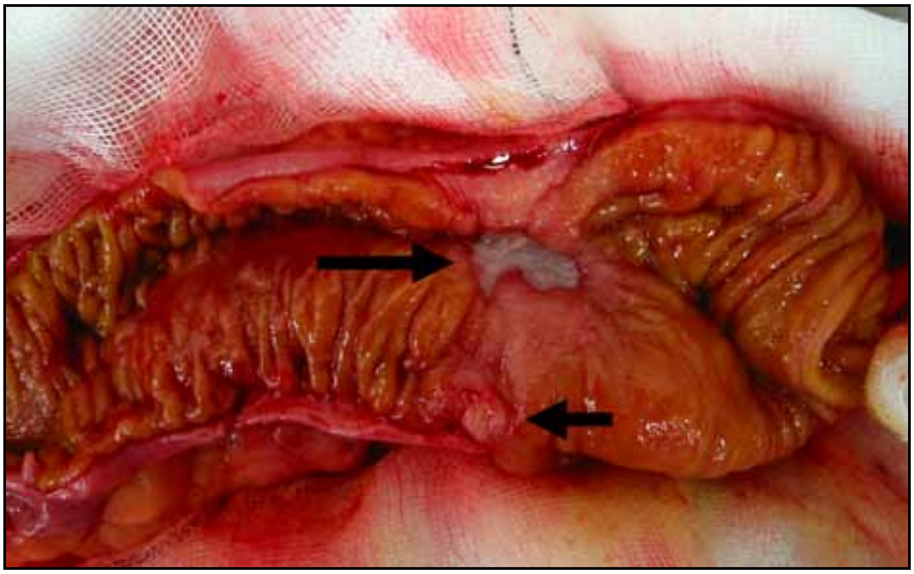

Figure 1. *Photograph of small intestine (opened longitudinally) showing neuroendocrine tumour. Short arrow shows the primary tumour, long arrow shows adjacent mesenteric nodal metastasis.*

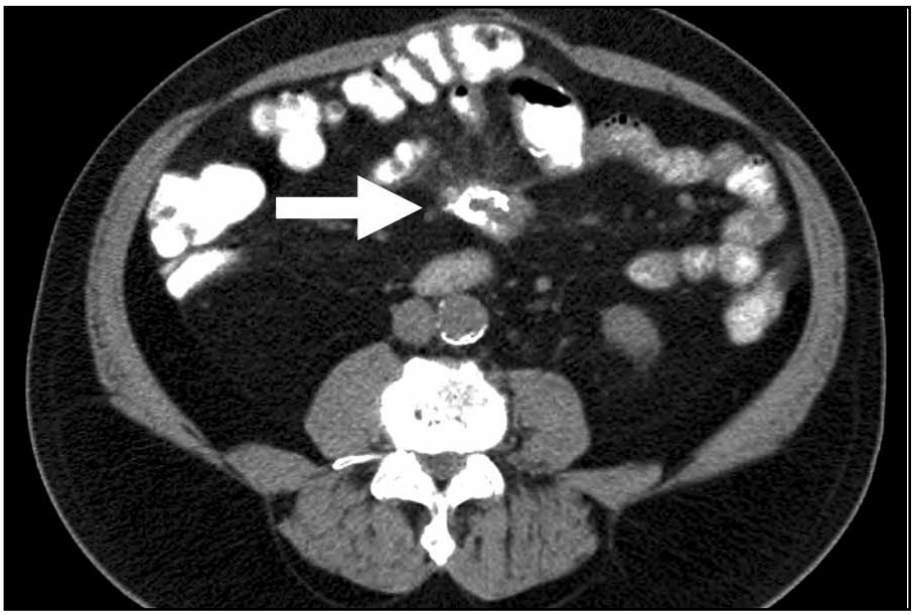

Figure 2. *CT appearance of a mesenteric metastasis from a small intestine neuroendocrine tumour (arrow) showing characteristic 'spoke and wheel' appearance due to surrounding desmoplastic reaction.*

Neuroendocrine tumours of the appendix

NETs of the appendix typically present as an incidental finding at the time of appendicectomy or other abdominal procedures. NETs are found in 0.2% of appendicectomy specimens on

histopathology and usually occur in the region of the tip of the appendix.[10] Patients with small primary tumours discovered incidentally may be cured by appendicectomy. The risk of metastatic disease to lymph nodes in the small bowel mesentery is related to the size of the primary tumour. Tumours less than 1cm have nodal metastases in up to 17% of cases, tumours 1 to 2cm in size have nodal metastases in up to 28% of cases and tumours greater than 2cm in size have nodal metastases in as many as 41% of cases.[11] The National Comprehensive Cancer Network recommends that patients with appendiceal NETs of size greater than 2cm should undergo right hemicolectomy to resect the mesenteric lymph nodes that may be involved with disease, however a recent study did not find a survival advantage associated with right hemicolectomy over simple appendicectomy alone.[11,12] Appendiceal NETs metastasize to the liver in only 9% of cases, and for this reason they are associated with excellent long-term survival with overall 10-year survival rates of 91-100%.[13]

Diagnosis and imaging of GI NETs

The investigation and staging of patients with GI NETs involves biochemical testing, cross sectional imaging and nuclear medicine studies **(Table 2)**. Patients with GI NETs should have 24-hour urine collection for 5-hydroxyindoleacetic acid (5-HIAA) to assess for the presence of carcinoid syndrome. 5-HIAA is the major breakdown product of serotonin that is excreted into the urine and its 24-hour urine measurement is a more reliable indicator of over-secretion of serotonin than serum levels of this hormone which may fluctuate. Where 5-HIAA is elevated or symptoms of the carcinoid syndrome are present, the patient should be assumed to have hepatic metastatic disease regardless of the results of imaging studies.[9] Serum levels of chromogranin-A, a glycoprotein with no hormonal activity that is incorporated within the secretory granules of NET cells, may be elevated in GI NETS from any site and the levels tend to correlate with tumour size and the extent of any metastatic disease. Chomogranin-A can be used as a tumour marker for GI NETs if elevated.

As most primary GI NETs are small in size regardless of site, they are rarely seen on cross-sectional imaging with CT or MRI. Imaging studies are more useful as staging investigations to detect metastatic involvement of mesenteric lymph nodes and/or the liver. The limitations of these modalities in the detection of small metastases should be recognized. CT and MR are useful in the detection of large mesenteric mass lesions, however will fail to detect smaller involved nodes in 16% of cases.[9] Similarly, due to the small size of hepatic NET metastases, CT and MR have a sensitivity of 77% and 82% respectively for the detection of these metastases.[9] In this way, negative imaging does not rule out hepatic metastatic disease in patients with GI NETs and underestimates the extent of metastatic involvement of the liver.

Nuclear medicine scanning is a useful adjunct to cross sectional imaging in the staging of NETs, and whole body nuclear medicine scanning may detect metastatic disease to sites outside the abdomen such as mediastinal nodes, the lungs and bone. GI NETs that express somatostatin receptors may be detected on radiolabelled octreotide scanning which has a sensitivity of 63% for detecting metastatic disease to the liver.[9] Whole body scanning with radiolabelled meta-iodobenzylguanidine (mIBG) can also be used in the staging of GI NETs and has a similar sensitivity to octreotide scanning for metastatic lesions. More recently, Gallium-labelled DOTATOC PET scanning has been introduced as a more sensitive staging investigation with some studies showing a sensitivity of close to 100% with this modality.[14] DOTATOC is a somatostatin analogue that is similar to octreotide but has a ten-times higher binding-affinity for somatostatin receptors on GI NETs. Standard PET scanning with 18-FDG is less likely to be positive in the setting of metastatic GI NETs due to their well-differentiated nature and is not recommended.

Regardless of the imaging modality employed, peritoneal metastatic disease from GI NETs is difficult to detect. Peritoneal metastases are found to be present at laparotomy in 25% of patients with small intestine NETs, yet can be detected on preoperative imaging in only 5% of cases.[9]

Table 2. *Suggested diagnostic and staging work up of patient with suspected gastrointestinal neuroendocrine tumour.*

Modality	Investigations
Biochemistry	24-hour urine 5-HIAA Serum chomogranin-A
Cross-sectional imaging	Computed tomography – Abdomen Magnetic resonance – Abdomen
Nuclear Medicine	Radiolabelled octreotide whole body scan Radiolabelled BIBG whole body scan Gallium-labelled DOATOC PET

Management of metastatic gastrointestinal neuroendocrine tumours

Where GI NETs have metastasized to lymph nodes of the small bowel mesentery creating mass lesions, surgical resection is indicated both to resect the primary tumour and the mesenteric nodal disease. This may be curative where distant metastatic disease is not present but also has an important palliative role in the relief of gastrointestinal obstruction and mesenteric vascular compromise.[15] Nodal mass lesions in the small bowel mesentery can be in close proximity to the superior mesenteric vessels or involving these structures, placing the vascular supply to the entire small bowel at risk during resection. Where these structures are involved with disease in the root of the small bowel mesentery, it may not be possible to completely resect the mass.

Where metastatic GI NETs express somatostatin receptors and demonstrate uptake on octreotide scanning, therapeutic radionuclide therapy with Lutetium-labelled octreotide can be administered as systemic therapy.[16] This treatment is currently available in Australia only in Melbourne and Perth. For GI NETs that demonstrate uptake on

mIBG scanning, therapeutic use of radioactive iodine-labelled mIBG can be similarly used and is available more widely.[16]

There are a number of therapeutic options for the management of hepatic metastases from GI NETs. Although none of the treatments offer the possibility of cure, they can be effective in controlling the symptoms associated with hormonal over-secretion and may prolong survival. Hepatic resection may be considered where it is estimated that 70-90% of total tumour volume can be resected.[15] This can be combined with ablative therapies directed to individual metastatic lesions, either at the time of open surgery or percutaneously under imaging guidance. Ablative therapies include radiofrequency ablation and cryotherapy. Embolisation of the hepatic artery with Yttrium-labelled microspheres can also be used to treat widespread hepatic metastatic disease from GI NETs that is not amenable to surgical treatment or ablation.[17]

Symptoms of hormonal over-secretion such as carcinoid syndrome can be effectively controlled by somatostatin analogue therapy. Well-differentiated GI NETs express receptors for somatostatin in more than 90% of cases and these act to inhibit NET cell secretion and growth when activated. The most commonly used somatostatin analogue is Octreotide, which is available in both short acting and long acting (Sandostatin-LARâ) preparations. Somatostatin analogue therapy is highly effective in controlling symptoms of diarrhoea and cutaneous flushing in patients with carcinoid syndrome with symptom control possible in 80-90% of cases and reduction in 5-HIAA levels in 96% of cases.[18] These agents may also have an inhibitory effect on tumour growth and can be associated with long periods of disease stabilization. Somatostatin analogue therapy is well tolerated but complications can include steatorrhoea (easily treated with oral pancreatic enzyme replacement), cholelithiasis and raised blood glucose levels.

Cytotoxic chemotherapy for metastatic GI NETs has previously used Streptozotocin-based regimens however these have been associated with limited efficacy. Newer targeted systemic therapies have emerged in recent years that show promise. The vascular endothelial growth factor (VEGF) receptor monoclonal antibody bevacizumab and tyrosine kinase inhibitors including sunitinib and sorafenib have all shown antitumor activity in phase II and III trials.[19] The mammalian target of rapamycin (mTOR) inhibitor everolimus has also demonstrated anti-tumour efficacy and is currently the subject of a phase III trial.

Even in the presence of hepatic metastatic disease, patients with GI NETs may survive for many years due to the relatively indolent nature of these tumours that are much less aggressive than carcinomas. Modern series of patients with metastic GI NETs show 5-year survival rates of more than 70% and median duration of survival from the time of diagnosis of nine years.[6, 15]

Management of neuroendocrine tumours at St Vincent's Hospital

The management of neuroendocrine tumours is complex and multidisciplinary and there is only a limited evidence-base with which to recommend treatments. For these reasons, a GI NETs multidisciplinary team meeting was commenced at St Vincent's Hospital in 2010 and meets on a monthly basis to discuss patient management and to make recommendations for ongoing patient care. The departments of surgical oncology, upper gastrointestinal surgery, endocrinology, medical oncology, chemical pathology, nuclear medicine and interventional radiology are all represented at this meeting. It is hoped that this meeting will improve the management of patients with these uncommon and complex tumours and provide a point of referral for the specialized care of these 'orphan' tumour groups within New South Wales and Australia.

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Diabetes treatment in 2011: GLP-1 receptor agonists and DPP-IV inhibitors

Dr Jerry Greenfield

Introduction

The last few years has witnessed the emergence of a number of novel medications that harness the glucagon-like peptide (GLP)-1 axis. These medications have been added to the growing list of agents available to target hyperglycaemia in type 2 diabetes. This article will discuss when these novel agents should be used, their mode of action and adverse effects and risks.

Diabetes treatment in the 'pre-GLP-1' era

The cornerstone of type 2 diabetes treatment has been, and will continue to be, weight loss. This is ideally achieved through diet and exercise, but may require the prescription of a very-low calorie diet and/or pharmacotherapy (with orlistat). Sibutramine was recently withdrawn from the market, due to its apparently adverse cardiovascular profile. The lack of effective weight-loss drugs available for prescription is a major impediment to inducing sustainable weight loss in the majority of patients.

The American Diabetes Association recommends that all overweight and obese patients with newly-diagnosed diabetes be started on metformin. Although not entirely established, metformin is thought to improve predominantly hepatic insulin sensitivity and reduce hepatic glucose production, particularly overnight (in the fasting state). One of the main advantages of metformin therapy is its association with weight neutrality, or even weight loss in some patients, which is in direct contrast to most other medications used to treat type 2 diabetes (particularly sulphonylureas and insulin). In addition, metformin has been definitively demonstrated to reduce the risk of diabetes complications (particularly microvascular disease in obese patients), have a beneficial effect on lipids and, more recently, reduce the risk of certain cancers. Although rare, cases of lactic acidosis have been reported in metformin-treated patients, particularly in the setting of renal impairment. The extended-release metformin preparation may aid adherence to therapy and may be associated with a lower risk of adverse gastrointestinal effects.

Despite the benefit of metformin on glycaemic control, a second agent is usually required after some time to control glycaemia. In the past, the only agents available were sulphonylureas (insulin secretagogues) or acarbose (alpha glucoside inhibitor), although the gastrointestinal side-effects (namely flatus) reported with the latter has limited it widespread use. More recently the thiazoladinediones (or 'glitazones') – PPARgamma agonists – have gained popularity. Rosiglitazone has attracted negative press in recent times, due to publication of meta-analyses reported a possible increased cardiovascular risk associated with its use. Pioglitazone is not thought to carry the same cardiovascular risk and may even be beneficial. The main advantage of the glitazones is their ability to induce durable improvements in glycaemic control up to many years. This is in contrast to most other oral agents, whereby initial improvements in

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glycaemic control are lost over time, leading to a progressive rise in glycated haemoglobin (HbA1c). However, the glitazones are associated with fluid retention, weight gain (partly fluid, mostly subcutaneous fat), an increased risk of fractures in men and women (particularly long bone fractures) and, rarely, worsening of macular oedema. Hence, their use needs to be individualised.

Repaglinide, a short-acting insulin secretagogue, is not PBS-listed for treatment of diabetes, but maybe particularly useful in patients with renal impairment.

The most effective method for improving glycaemia in type 2 diabetes is insulin. Various regimens can be used, often in combination with oral agents (especially metformin, in order to limit weight gain).

GLP-1 PHYSIOLOGY

GLP-1 is one of two incretin hormones (the other is GIP) that control insulin release after a meal. Exenatide is an injectable GLP-1 receptor agonist, recently made available for the treatment of type 2 diabetes. In 1992, exendin-IV, which has a ~50% sequence homology to human GLP-1, was isolated from the venom of the Gila monster, a poisonous lizard that lives in the deserts of Arizona **(Figure 1)**. Exenatide is a synthetic version of exendin-IV that is resistant to the normally rapid (within minutes) inactivation of GLP-1 by the enzyme dipeptidyl peptidase (DPP-IV) in the circulation. GLP-1 has a number of beneficial actions, including its ability to increase insulin secretion (in a glucose-dependent manner), inhibit glucagon secretion (the main hormone that increases liver glucose production), increase satiety and slow gastric emptying **(Figure 2)**. No other currently-available diabetes medication is able to reduce hyperglucagonaemia.

Figure 1. *The Gila monster (Heloderma suspectum)*

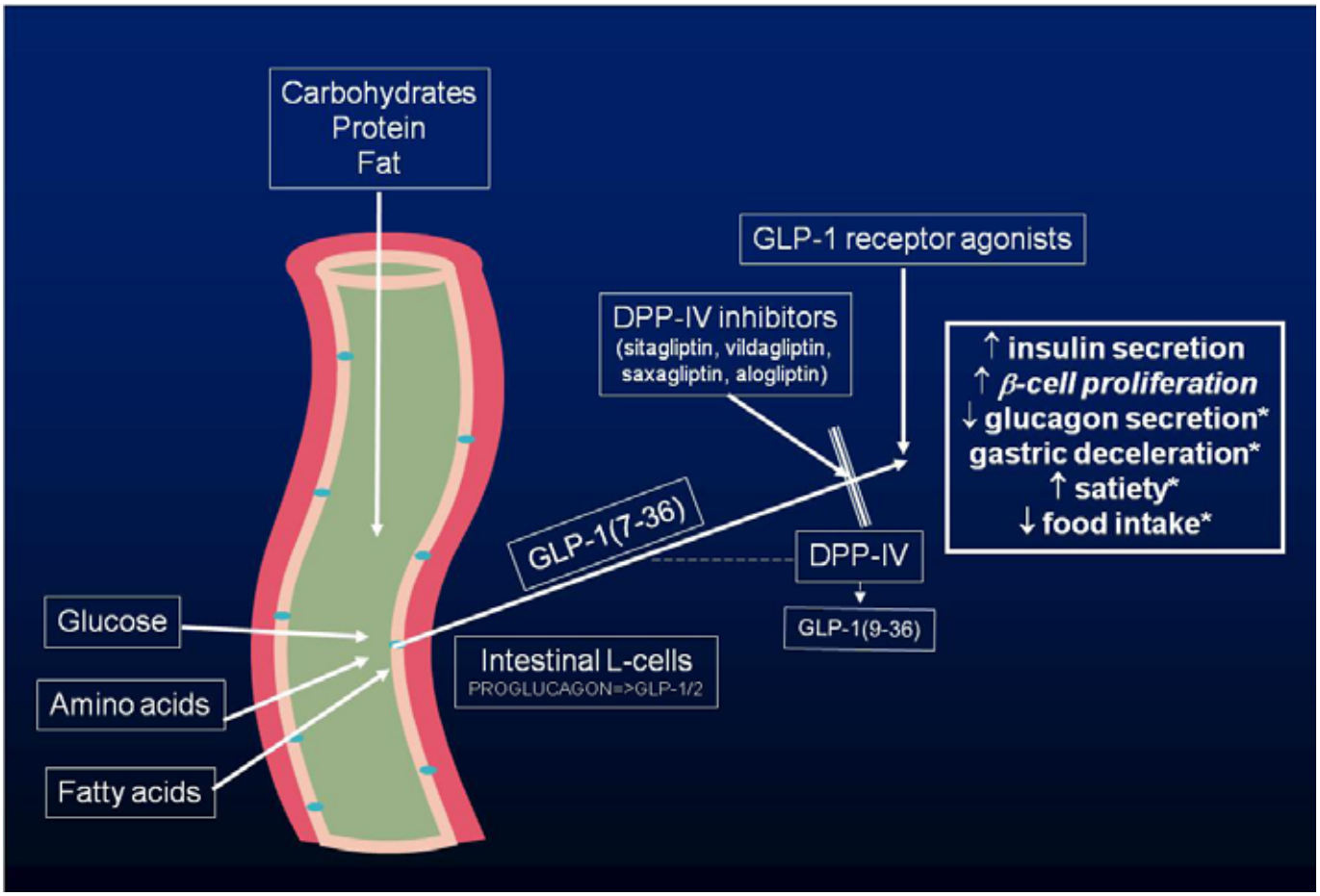


Figure 2. *GLP-1 secretion and action.*

In type 2 diabetes, the GLP-1 response to a meal is reduced. This has led to the development of agents that target this pathway and increase GLP-1 levels and/or action. The two approaches that have been taken have led to the development of the GLP-1 receptor agonists and the DPP-IV inhibitors.

GLP-1 receptor agonists

Exenatide, a GLP-1 analogue or receptor agonist, is administered twice daily via the subcutaneous route. Newer GLP-1 receptor agonists, that can be administered weekly or even monthly, are in development. Exenatide is PBS-listed for add-on therapy to metformin or sulphonylurea treatment (or both) for patients with HbA1c > 7%. It is not PBS-listed for use with insulin. The starting dose is 5 mcg bd, increasing to 10 mcg bd after one month if tolerated. The main advantages of exenatide compared to sulphonylureas and insulin include: (i) its association with a lower risk of hypoglycaemia, due to its induction of insulin secretion in a glucose-dependent manner (ie. when glucose level is high, not when it is low or normal); and (ii) its ability to induce weight loss (due to effects on appetite and gastric empyting), which is up to 4-5 kg or more in some patients. The main adverse effect of exenatide is nausea, although this usually improves with time. Weight loss is independent of the development of nausea. In our experience, nausea precludes long term use of exenatide in up to one third of patients. Isolated cases of pancreatitis and renal impairment have been reported in patients treated with exenatide. Exenatide should not be used in patients with gastroparesis, due to its effect on gastric emptying.

DPP-IV inhibitors

The other group of agents that target the GLP-1 pathway are the DPP-IV inhibitors. DPP-IV inhibitors are taken orally. The currently available DPP-IV inhibitors in Australia are sitaglipin, vildagliptin and, most recently, saxagliptin. Gliptins are PBS-indicated for use with either metformin or a sulfonylurea, when one of the two of these medications is either not tolerated or contraindicated and glycaemia is suboptimally controlled. These drugs are not PBS-listed for single or triple therapy (ie. with both metformin and a sulfonylurea) or for use with insulin. The dose of sitaglipin should be reduced in patients with renal impairment; it is best avoided in patients with eGFR <30ml/min/1.73m2. Vildagliptin is contraindicated in significant liver disease and mandates regular liver function test monitoring for the first year of use in all patients. These agents are generally well tolerated, although some patients describe nasal stuffiness. DPP-IV inhibitors do not slow gastric emptying and are weight-neutral (as the active GLP-1 levels attained and subsequent GLP-1 receptor activation are orders of magnitude less than that observed with GLP-1 receptor agonists). There may also be an increased risk of pancreatitis with the DPP-IV inhibitors.

When to use exenatide and the DPP-IV inhibitors

As mentioned, these agents are generally used second or third line in diabetes treatment (ie. added to single- or dual-agent regimens). Generally speaking, these agents should be used in patients whose HbA1c is 1-2% above the desired target, considering that they only lead to modest reductions in glycaemic control. They are not generally suitable for patient whose HbA1c is >9%, as it is unlikely that they will lead to achievement of glycaemic targets. An exception to this is in patients who lose weight with exenatide, in whom glycaemic control may improve more significantly due to the effects of weight loss itself.

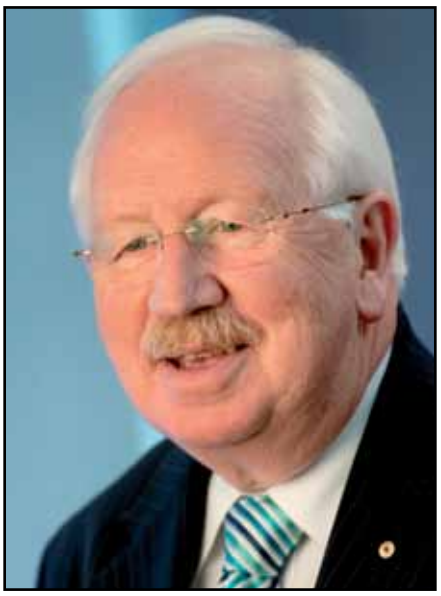
It is likely that these agents will have their greatest benefit early in the treatment of type 2 diabetes, considering that they enhance insulin secretion, which becomes relatively impaired over time. Whether the glycaemic benefit observed with these agents is sustainable over time is yet to be determined. Furthermore, the long-term safety of these agents, particularly in relation to cardiovascular disease risk, is yet to be shown.

Conclusion

The addition of the GLP-1 receptor agonists and the DPP-IV inhibitors has widened the available treatment options for type 2 diabetes. The development of effective glucose-lowering agents that limit weight gain, and even lead to weight loss, are appropriate add-on therapies in some patients, and may delay the need for insulin treatment.

The Sandra David Oration

Quality in health – Belief, Care and Passion?



Prof Clifford Hughes AO

History of St Vincent's Clinic Foundation

During my research for tonight, I was fascinated to discover that St Vincent's Clinic Foundation was the vision of Sr Mary Bernice Elphick RSC and the founding doctors of St Vincent's Clinic. Sr Bernice was to write, "The value of the latest developments on treatment and procedures can only be tested by clinical practitioners and based on their detailed outcome studies of actual patient care. However, although government and other research organisations provide financial support for basic laboratory work for full-time investigators, there is little funding available for clinical studies conducted in the course of patient care. Yet it is this evaluation on which all new treatment modalities rely".

I note that the three aims of St Vincent's Clinic – patient care, medical teaching and clinical research – are symbolised in its logo by three separate and interwoven triangles of equal size.

Sandra David (1934 – 1994)

Sandra was born in 1934, the eldest daughter of Joe and Edith David, in a family of 12 children. As the first daughter after four sons, she quickly learnt to hold her own! She developed a shy, but outgoing nature and was described as a "free spirit".

Family life and Christian values were very strong. She was educated by the Sisters of Charity at St Vincent's College, Potts Point, later entering their congregation

After teaching in Australia, Sandra joined her missionary brother, Max teaching in the New Guinea Highlands, where she was known to walk two days to the more remote villages. She always made sure her charges had enough to eat and could tend their own gardens.

On her return to Australia, Sandra, now known for her tenacity (described by some as stubbornness), joined the family company – working with two of her brothers, John and Peter. To quote John "We should have taken more notice of her".

Diagnosed with breast cancer when only 50, she fought bravely, but secondary brain tumours developed three years later. Her endurance, devotion to duty and commitment were values she held dearly. During her illness she had an opportunity to discuss this oration with Sr Bernice and expressed agreement with the concept and its purpose.

Sandra David died peacefully on 13 September 1994. RIP and she is mourned and remembered by all who had the privilege of knowing and working with her.

So, with that prologue, I would like to thank the St Vincent's Clinic Foundation for inviting me to this platform this evening. We have acknowledged two great women, and in addressing the issues of quality in health, I would like to start by acknowledging the work of a third, Florence Nightingale.

Florence Nightingale lived in extraordinary times and did extraordinary things. "The Lady of the Lamp" conjures up, even through the mists of time, an image of care beyond the ordinary and a drive to improve that **care** was more than personal. She **believed that** what she was doing was the right thing to do and, as a consequence, stood up to the generals, the military surgeons, and indeed, society with a strength rarely seen since. For Nightingale had a **passion** for her cause.

At the Sydney Hospital, there is a building named in her honour. It was built with her support and guidance. The early nursing staff were inspired by her letters, suggestions and forthright instructions for health care. So I will focus on those same three aspects of health care – **Belief, Care** and **Passion**.

Sir Liam Donaldson, when Chief Medical Officer for the National Health Service in the UK defined clinical governance as "a framework through which … organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care, by creating an environment in which excellence in clinical care will flourish". (Scally and Donaldson, 1998)

In 2004, the then Premier of NSW, Morris Iemma announced the formation of the Clinical Excellence Commission, as part of the NSW Patient Safety and Clinical Quality programme. The foundation had been set up by my predecessor, Professor Ian O'Rourke, CEO of the Institute for Clinical Excellence. Sadly, he too fell victim to cancer. His legacy also survives.

The **Mission** of the Clinical Excellence Commission is "to build

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confidence in health care in NSW by making it demonstrably better and safer for patients and a more rewarding work place". We have, therefore, two planes of focus - our patients and our staff. Tonight I would like to recognise the excellent care provided by NSW health care workers and to issue a challenge to follow the examples of the three women I mentioned earlier.

Belief

The Oxford English Dictionary describes belief as "a person's religion or religious conviction" or "a firm opinion" and "an acceptance of a thing, a fact or a statement", "trust or confidence in something or someone".

It is certainly true that there are many in health who are there because of a strong religious conviction of God's calling for them. I am one of those people. But there are many others who are there because they have a strong belief in compassion and care and in the systems necessary to deliver both. Altruism is not unusual in our staff, at least in the beginning, but do we foster that selflessness? Do we encourage the young idealists to continue their crusade? Do we really make health care a more rewarding workplace?

There can be little doubt that society, technology and health infrastructure has changed dramatically. Our community is ageing rapidly, but there is an even more dramatic ageing of patients in acute care facilities worldwide. Simply put, there is more work to do.

Technology lets us do much more than we dreamed possible. Gene therapy, chemotherapy, minimally invasive procedures and extraordinary intensive care support facilities are almost taken for granted, but these are expensive weapons. In short, it costs more.

There's a growing demand for health services. There's also demand for better public housing, better transport, better education. So strong is that demand that we could rewrite the "rights of man" as education, health, long life, accommodation, transport and recreation. In developing countries plagued by drought, flood, famine and disease, these are often only aspirations. Shortage of medical, nursing and allied health staff threatens all health care systems. But the disparity between rich and poor also poses a problem for health care in the developed world. We can no longer pillage nursing and medical staff from the third world, by offering them well-paid jobs to treat the few, while the masses continue to suffer.

So do we believe that we can do it better? Do we believe that we can change the system? Do we believe that there are areas that need urgent change? I believe that the answer is a resounding "yes" and I can base that answer on some evidence from our work at the CEC.

One of our tasks was to develop a **Quality Systems Assessment** program: to know what systems were in place to ensure the highest quality of care. We began by examining the "high-reliability" industries – nuclear, oil, aviation, rail, shipping and mining. They all have two things in common. They constantly monitor their own systems and they have strong reporting cultures. There is a third – whenever things go wrong they appear on the front page.

The QSA is an electronic self-lodgement of system data provided by three layers of the system – area health services at an executive level, facilities at a management level and clinical units at the level of head of department or nursing unit manager. We have completed two reviews and validated the responses. The results are truly remarkable and demonstrate the **belief** of our staff in what they are doing. The response was greater than 90 per cent in each level.

Validation was equally amazing. We had asked units to source evidence to support their self-assessment. Each was expected to provide actual evidence of their activities to the onsite assessors. The accuracy rate was 98.6 per cent. Approximately 10 percent of these inaccuracies were because a question was misunderstood. Where there were discrepancies, half had overestimated and one third had actually underestimated performance.

Why should these results be so complete and accurate? It is my hypothesis that the system wanted to know how good (or bad) they were and, where they were not so good, how bad they were. Because they received feedback so promptly, staff had a strong belief in their own capacity to improve. In fact, all respondents had already reported improvements to their peak quality committee. Finally, because they wanted to use the information, there was no point in self-deception.

Another major task was to support the **Incident Information Management System**. A unique opportunity presented itself in the first two months of my tenure. I was able to "buy" the raw, unfiltered incident data provided by an on-line system accessible to all staff. Any incident could now be notified anonymously. That $2 million "investment" has reaped enormous dividends. (It is similar to the Riskman program used here at St Vincent's).

Far from being distrustful, suspicious and protective, our staff continued to increase reporting rates over the last six years. We now receive over 16,000 incident reports per month. Before you panic, 0.5 per cent of these are severe events, that is a rate of 0.04 per cent of all hospital admissions. More than 91 percent of the incidents notified are associated with minimal or no harm.

So what does this tell us? Our staff believe in the excellence of care and even report "near-misses." In reality, this is a misnomer. They are actually "good catches". For example, a nurse at the pre-operative check identifies a potential wrong patient procedure, or a cross-checking of a unit of blood prevents an inappropriate transfusion. Both were reported, even though an adverse event had been prevented. Now we could identify and remedy the causal factors. Our staff have a strong belief in their ability to improve the system. There is no need to hide!

Care

How well do we really care? One of the remarkable strengths of Florence Nightingale was her emphasis on measurement. Long before her surgical colleagues were reporting their own performance, she was admonishing her staff to keep records to review the outcomes, and was able to take information on survival of battle

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casualties to the generals. More people were dying of infections than were dying of battle-related injuries. So if we are to care, we need to measure our care.

In his review of acute care services in NSW, Peter Garling SC had strong words to say about hand hygiene. He said, and I quote, "anything less than 100 per cent compliance is, in my view, unacceptable" and recommended sanctions for those who chose not to follow.

The CEC embarked upon a hand hygiene program entitled **"Clean Hands Saves Lives".** In a range of hospitals, we set up an audit program and watched what staff did while treating their patients. The results were quite frightening. Doctors were the worst (30 per cent compliance, versus 52 per cent for nurses). All staff performed more hand hygiene after they had been in contact with a patient than before. The message was clear. "You, Mrs Jones are the dirty one!"

It belies belief that staff did not wash their hands, but they are as human as the rest of us. Let me ask you some questions, not to excuse bad behaviour but to understand it. Do you always wash your hands before a meal? Do you wash your hands after you pat a dog? One interesting fact emerged from our review. People are more likely to wash their hands after they pat a stranger's dog than after they pat their own dog. Familiarity can breed contempt! So before we become too judgemental, let's have a look at some of these factors.

Soap and water techniques were harsh, caused drying of the skin, caused reactions and could even damage the skin of the health care worker. Basins and soap were a long way away from the patient, often outside the room. A two-minute wash meant that the average nurse was spending, literally, hours at the sink.

We introduced alcohol-based hand rubs (or gels) and an education campaign in every hospital in NSW. The risk of staff-spread infection reduced. We cannot prove "cause and effect", but hospitals with the best compliance had the greatest fall in infection rates. The alcohol-based rubs were kinder and gentler on hands. A fifteen-second hand rub meant that a nurse could save 58 minutes a shift. Now there's some time to talk with a patient! What administrator wouldn't love to have an extra hour per shift of a nurse's time? Way and beyond all that, who of us wouldn't feel more confident in the nurse, the doctor, the wardsman, the orderly, or indeed the manager who approached us rubbing the gel on their hands? You see, care is more than just belief, it is actually action based on evidence.

The program has been very successful. The most recent survey in NSW demonstrated that compliance rose to 75 per cent for nurses and 50 per cent for doctors. Great work. We've doubled the compliance, but we have a long way to go if we are to truly care.

A second project that has identified the benefits of measuring our care is Blood Watch. International estimates suggest that as much as 30 per cent of blood is used inappropriately in elective surgery. That is not only a waste, but is frankly dangerous: any complication (e.g., hepatitis C) after an unnecessary procedure is, by definition, an avoidable adverse event.

We needed to understand why blood was prescribed. Marketing consultants analysed prescribing practices - it was clear that there was very little evidence base to age-old protocols. Junior staff often transfused because they thought their consultant wanted a particular haemoglobin level. The unit did not have a protocol. Guidelines from the National Health and Medical Research Council (NH&MRC) were not being used at all! Yet they were remarkably simple. If a patient's haemoglobin level is below 7g/L, then they really ought to have a blood transfusion. If the haemoglobin is greater than 10g/L, there was no evidence in the literature that a transfusion would be of benefit (unless the patient was actively bleeding). But with the haemoglobin between 7 and 10g/L, transfusion is of real use only if the patient has symptoms or signs related to their anaemia.

Linked data from the Department of Health, the Australian Red Cross Blood Service and local transfusion committees varied greatly. In one instance, a hospital was giving 80 per cent more blood than peer group facilities.

We had presented the data at 8 pm at a dinner meeting of all staff. At 9 am the next day, just before Grand Rounds, the chair of the transfusion committee told me they had solved the problem. I thought that was pretty quick, so how did they do it? "Well, we had a look at our process. The pathology laboratory staff, not the haematologists, were instructed to ring the intern if the haemoglobin was below 9g/L". Now, if you are young intern only three months in a country rotation and you get a call at 2 o'clock in the morning, saying Mrs Jones haemoglobin level is 9g/L, what do you do? You order two units of blood. The hospital adopted the NH&MRC guidelines and blood usage plummeted.

You can participate in this at an interactive website, The Transfusion Question, at www.transfusionquestion.com

Local programs have meant that blood usage in NSW reduced by 10 percent. We reduced the waste, we reduced the risks of transfusion complications and surgeons identified patients at risk of a transfusion prior to admission. This allowed anaemia to be corrected before surgery, with oral iron supplements dramatically reducing the chance and risk of transfusion.

There were also economic benefits. We saved the NSW health budget in excess of $2 million per year. People changed behaviours because they do care. We just needed to provide evidence of their performance.

But change will not happen just because it's a good idea. We need to re-engender, re-enthuse and re-awaken the passion that caused us all to join the caring professions.

Passion

The Oxford Dictionary defines passion as "a strong and barely controllable emotion", or "a strong enthusiasm"', and "the thing arousing this enthusiasm". I still remember the excitement, the enthusiasm of my first day on the wards. "This is what I want to do. This is what I want to be." But I also remember how quickly some of that enthusiasm was squashed by the offhand comment – "well, we don't do it that way" or "you

The Sandra David Oration

can't do that" or "why are you bothering me?". Those pressures are all too real in a busy hospital, particularly when senior staff, often tested to capacity, tired and even demoralised, throw a wet blanket on the fire of youth.

One of the greatest risks for our patients is unrecognised deterioration on the ward. This quiet demise is a worldwide problem. The patient who is supposed to be under our care slips away quietly and unnoticed, until it is too late. Very few survive a cardiac arrest call. We must reinvigorate our early passion to wash our hands, to do the observations both regularly and carefully and to listen to the patient. Recall the passion to do the simple things well and passion to call for help when things aren't quite right.

The tragic story of Vanessa Anderson, who died after being struck by a golf ball, led the State Coroner to highlight these issues. Observations were not taken, concerns were not escalated to more senior personnel and no one escaped the tragedy. But what if the staff had maintained their enthusiasm for taking the pulse, for measuring the blood pressure, or more particularly, for recording the respiratory rate?

The CEC had begun a series of diagnostics across the State. We found that of the five indicators of deterioration, most (pulse rate, temperature, blood pressure, the level of oxygen in the blood) were collected from the monitor in a matter of seconds. But the fifth, respiratory rate, was being recorded in only 11 per cent of our patients – because it took time. It took a minute to stand by the bed and watch the person's chest rise and fall, yet every mother knew that, when Jane or Johnny was breathing fast, there was something wrong, and every partner knew that, when an elderly patient with respiratory disease was breathing fast or breathing slow and laboured, something was wrong. Even technology, or our reliance on it, blunted our passion for individual patient care.

I agonised over this problem long and hard. Whilst on a beach at Forster and preparing for a talk on clinical guidelines, I took photographs of various warning signs around the town. I included the red and yellow flag of the Surf Life Saving Association of Australia (SLSA) and wondered how effective they were. The SLSA explained that, since they had been collecting records from the late 1930s, there had not been a single death from drowning for swimmers between the flags on a patrolled beach. Then the penny dropped. Lifesavers, all passionate young men and women, spent their entire time on the beach watching swimmers. One lifesaver on Bondi Rescue said "if you wait until they wave their hands, it's often too late".

So, with their permission, we adopted this approach. We introduced a program called **"Between the Flags"** and a simple colour coded chart. The five main observations are clearly recorded. Staff just put a dot into the right box. The trend is obvious and if it goes into the yellow zone, they are prompted to act and to consult with their seniors. The chart actually authorises them to call for help. If the observations stray into the red zone, you are immediately prompted to call a Medical Emergency Team or equivalent backup (even a paramedic team in some country towns!)

This became one of the biggest culture change movements in the public health system in NSW. The chart was mandated in all facilities from 15 January 2010. All facilities had to have an escalation process, so that junior staff members were no longer alone and all staff members felt empowered to call for help.

There has been a dramatic change. Nurses have excitedly told us that they can call for help and that they no longer feel alone. Young doctors, concerned about an increased workload, realised that they too were liberated. They could make early decisions and, if necessary, call their consultant or a medical emergency response. This is what they always wanted to do, and other staff caught the vision and the passion.

But this is not rocket science. We have simply changed the environment – allowing staff to express their **passion** for the **care** of patients whom they **believe** they are here to serve.

So why tell you all this? Many of you will have read Malcolm Gladwell's treatise, "The Tipping Point" and, in particular, the amazing story of the clean-up of New York. The wave of violent crime was stemmed when Mayor Giuliani and a subway director, David Gunn, decided to stamp out graffiti and fare evasion. Fixing these minor infringements brought about a dramatic and persistent reduction in violent crime. They had unlocked the "Broken Window" theory and the principles of Order and Disorder. We need to rediscover both if we are to bring about change in our health systems. Gladwell refers to several experiments carried out by Dr Keiser et al in the Netherlands.

One was conducted in a factory, where researchers painted a sidewall in the alley where staff parked their bikes. They then put a "no graffiti" sign on the wall and taped a notice to the handlebars of each bike, saying words to the effect "Welcome to work today. We hope you like the way we have tidied up your parking area. Please keep it tidy and have a good day". There were no bins in the alley. The notices had to be removed before staff could ride home. In phase 1of the experiment, nearly 80 per cent of the staff rode off with the paper. In phase 2, just a few months later, they made one small change. They put some graffiti on the wall. This time, the majority of staff threw the pieces of paper on the road and rode away.

We are all conscious of order and even more so, of disorder, in previously ordered systems. That is the "Broken Window". The staff in the factory felt that if it was okay to break the "no graffiti", then it was okay to litter.

So, if it's okay not to record an observation, or if it's okay to waste blood, or if it's okay not to wash your hands occasionally, why are we not surprised if the reality of disorder spreads through our wards? Clinicians are no different from the rest of society.

Florence Nightingale brought order to nursing. She believed that she could bring about change. She shone a caring light into the darkness. And she was passionate about her cause.

I began with the three triangles in your logo, Patient Care, Medical Teaching and Clinical Research. We took heart from the work of three inspirational women. Together we examined the impact of just three human attributes, Belief, Care and Passion in improving patient care, evident in the work of the Clinical Excellence Commission. Each attribute has a major impact of itself, but, woven together, they become a "thrice-stranded cord" which, said King Solomon "is not quickly broken".

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