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St Vincent's Clinic

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St Vincent's Hospital

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

EDITORIAL

Dr John O'Neill MD, FRACP

Consultant Neurologist

Editor, *Proceedings*

This is the 25th issue of *Proceedings*. The Sandra David Oration for 2012 was given by Mr David Gonski AC. His 2012 report (commissioned in 2010) reviewed performance and funding within the Australian School System and its release made political headlines. The findings, as highlighted in the Oration, are summarised in this Issue. It is the hope of those responsible for the report that the proposed arrangements will deliver a funding system that is transparent, equitable and financially sustainable as well as being affective in providing an excellent education for all Australian students.

The St Vincent's Clinic Foundation has this year provided $754,000 in research grants and awards. The recipients of these grants and their topics of research are shown on pages 32-33.

This year, I would like to make special acknowledgement of Mr Ted Harris AC who has been the Trustee of the Foundation since 1993 and its President since its formal inauguration in 2000. Only this year he was made a General Member of the Sport Australia Hall of Fame.

Professor David Ma, haematologist, was recipient of the Foundation's major award, the St Vincent's Private Hospital Ladies' Committee Sister Mary Bernice research grant in 2012. In this Issue, he and Clinical Research Fellow, Dr Grace Gifford provide an excellent overview of the recent benefits of research applied to the treatment of various haematological malignancies (leukaemia, lymphoma and myeloma) with an associated greatly improved prognosis in those conditions.

Dr Max Coleman, a now retired eminent St Vincent's gastrointestinal surgeon, has remained active in research, particularly with respect to the surgical history of St Vincent's Hospital. His article describes the characters and events around the infamous "Bible Incident" at St Vincent's in 1859.

Associate Professor Katherine Samaras, endocrinologist (also a past recipient of the Ladies Committee Sr Mary Bernice research grant) writes on the importance of active prevention and treatment of obesity, now epidemic amongst the Australian population. She particularly highlights the obesity endemic in our psychiatric population wherein there can be a twenty year shortfall in life expectancy, predominantly due to cardiovascular disease and diabetes and both related to obesity in that population.

The Vascular Laboratory at St Vincent's Clinic offers top class diagnostic studies. In their article, Ms Debbie Hamilton, scientist and Dr Michael McGrath, vascular physician have reviewed the unusual and interesting, non-atherosclerotic causes of external iliac artery stenosis which have been identified in the Clinic over recent years.

In a short review, Associate Professor Debbie Marriott, microbiologist describes the importance of prudent antibiotic usage in hospital patients, especially the complex patients seen in intensive care. As a first in NSW, significantly more rational antibiotic usage has been achieved by the development at St Vincents of therapeutic drug monitoring in the important Beta-lactam class of antibiotics.

One of the most rigorous and prolonged professional training courses in Australia is that to qualify as a Clinical Neuropsychologist. So what do these people do? This question is at least in part answered by Dr Jeannette Stewart in her review of the methods and applications of Clinical Neuropsychology in the medical and legal settings.

Finally, Associate Professor Ian Woodgate and Dr Oliver Koo, orthopaedic surgeons present the largest series in the literature on the surgical management of sacro-iliac disease, an often unrecognised cause of low back pain.

The Sandra David Oration

More Funding for Australian School Education

Why did a Labor government choose a resident of Point Piper, a dreaded merchant banker, educated at a private school, chaired a private school for eight years, sat on the board of that school for 18 years, and not an educational professional, to review the funding of school education in Australia?

The short answer is I don't really know.

However, I wonder whether it was because Julia Gillard realised that I came from a family of serial immigrants who realised the importance and potency of education.

In my case, my grandfather went to South Africa from Poland and suffered as he did not have an education or a skill. He sold material door to door and struggled through until the day he died.

Only one generation later my father, an educated brain surgeon, migrated to Australia and the ease with which he fitted in to this community and the comparative luxury which we enjoyed is proof in itself of the effect that education can have on a person and a family.

Perhaps she also realised that as a businessman, my biggest worry for Australia is falling productivity and that I adamantly believe that education is the single best factor to improve a country's productivity – although I acknowledge it doesn't have an immediate effect.

Mr Gonski is Chairman of Investec Bank (Australia) Limited (the Australian subsidiary of Investec Bank PLC), the Guardians of the Future Fund, Coca-Cola Amatil Limited and Ingeus Ltd. He is also Chancellor of the University of New South Wales, Chairman of the National E Health Transition Authority Ltd, the UNSW Foundation Ltd, Swiss Re Life & Health Australia Ltd and the Sydney Theatre Company.

Mr David Gonski AC

Whatever the reason it was an honour to be chosen and particularly so considering the overwhelming importance of good school education.

From the approximately 80 organisations and schools the review visited and talked to and the more than 7000 submissions it received, I and my fellow reviewers learnt:

a. Australia has a good school education system but whereas ten years ago we were internationally one of the top performers, now we are being beaten by the entry of South East Asian nations and also by other countries like Finland which regard education as important. This can be seen by comparing the PISA scores of ten years ago to more recent ones. Australia is slipping.

b. There is a growing tail between those who suffer disadvantage and those who don't and this seems totally unjust.

This led the review to define what we believed as "equity" and our mantra there was that we wanted to create a funding system that ensured differences in educational outcomes are not the result of differences in wealth, income, power or possessions.

c. It is not just financial disadvantage that can cause differences in educational outcomes.

If you are indigenous your chance of getting to Year 12 is materially less than for the rest of the population.

If you live in a remote area your chance of great educational achievement is also less.

Having English not as a first language can also have an adverse effect on educational outcomes.

d. The emotion in relation to whether government should fund both

government and non-government schools still exists in some quarters. The horse, however, has well and truly bolted. There was at the time of the review approximately 3.5 million students at school in Australia. 35% of them attend non-government schools. In some areas one out of two students goes to a non-government high school.

e. Spending on school education in Australia in the year 2014 will reach the sum of $1 billion a week from all sources.

The Federal Government in 2009 spent approximately 80% of the money it spends on schools on non-government schools. Often this number is used to show how unfair that is to government schools. What that argument ignores is that each of the Australian states spend 90% of their funding for schools in their government school's systems.

Overall 30% of total government funding in Australia in 2009 for schools came from the commonwealth and 70% from the states.

f. The school funding mechanisms in Australia working at the time of the review were not transparent and not well understood nor well articulated.

Non-government schools got funding based on the cost of government schools which often is not a true comparison.

g. Disabled children in 2009 could only go to government schools if government funding is to be given. The concept that they should not have a choice but the rest of the population does is very sad indeed and does not endorse Australia as having the open and understanding culture it should.

h. The decision to build new schools is entirely arbitrary. If someone has a good idea that a school should be built there is very little coordination between government and non-government sources to determine, for example, what sort of school it should be. This results at times in existing schools being over full and new ones empty.

Our review team learnt even more than this but I will mention only one more thing – we learnt that the difference between many faith-based schools and some government schools and indeed the difference between the better government schools and the not so good government schools was often community involvement. Where the community loved their school and nurtured it, it did better.

The dreams of our lengthy report can be summarised as follows:

a. We advocated that the federal government and the state governments should fund together rather than one substantially funding non-government schools and the other government schools.

b. That in making this funding, governments should find a standard (a new resource standard) that is based on aspiration (i.e. what we want to achieve for our children not what it costs government to achieve what they are achieving now).

We took an aspirational measure to start with based on NAPLAN results which only 16% of schools achieved at the time.

c. We dreamt that funding should allow for loadings to assist:

– where there are indigenous students;

– where there are disabled students;

– where there is social financial disadvantage;

– where there is remoteness; and/or

– where English is not the first language.

d. We suggested that government schools should be fully funded by government.Also special schools (say for the disabled, etc.) should be funded in that way. We suggested that non-government schools should be funded between 20% and 90% of the resource standard and that the difference between the 20 and the 90 should be based on what we called a capacity to pay. This we suggested in the first instance should be determined by looking at the socioeconomic status (SES)numbers from the census but if a better way of calculating capacity to pay could be found, we would favour a change.

e. We advocated that the disabled should have their funding portable so that they can choose whatever school they wish to attend.

f. Most controversially, we suggested that further money would need to be spent on education. You will have seen that we suggested an increase of $5 billion on what was spent in 2009 (paid by federal and state governments in a proportion to be negotiated by them). This was an increase of 15% and less than half a percent of the GDP of Australia at that time. We noted in making this recommendation that money cannot fix all but that we were convinced that more was necessary.

g. We advocated transparency with a separate and independent group working out what should be paid to schools. We advocated a system for working out where new schools should be built and when and indeed with whom they should be associated. We also advocated further capital payments for government schools.

We also made other recommendations:

a. Community involvement we saw as very important in schooling.

b. We noted that the mechanisms to promote philanthropy to schools do not generally exist and particularly in relation to government schools. Many schools do not have the ability to chase philanthropic monies nor the experience to do so.

So, a fund or funds should be established for donations to schools and through this or separately government should assist both government and nongovernment schools to increase their capacity to get development officers, etc., to raise funds.

c. We also suggested autonomy for Principals, boards for government schools and peer review to name but a few.

For a more productive Australia and because of what it can do for individuals – we need so much of this.

It is obvious from reading the history of Sandra David that she knew the importance of a good education. She undoubtedly also knew that those, whether they be in Papua New Guinea or here in NSW, who didn't get a good school education would not have the productive and enjoyable life of those who did.

Dr Grace Gifford
Professor David D Ma

Use of non-cytotoxic drugs and immunotherapy in the treatment of haematological malignancies – a changing paradigm

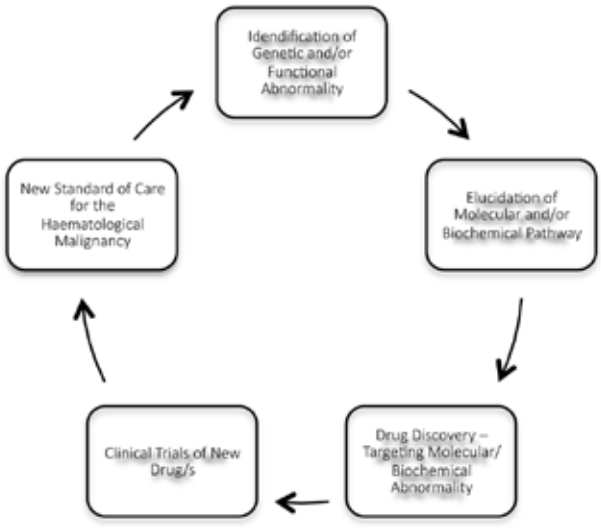
Introduction

Haematological malignancies are the commonest malignancies affecting children and young adults. In adults, lymphomas are the sixth most common cancer and about 3000 Australians are diagnosed with leukaemia annually.

Cytotoxic chemotherapy had been the main treatment modality but advances in the molecular pathology of haematological cancers have led to the discovery of target specific, non-cytotoxic therapies for these malignancies (Figure A). These new drugs are efficacious and have usually tolerable side effects. These new drugs reduce and, in some cases, replace the use of conventional chemotherapy leading to improved survival and quality of life (QOL).

The Haematology Department of St Vincent's Hospital has been at the forefront in research in this field, establishing new standards of care for these life-limiting malignancies. In this article, we summarise recent key treatment advances that are in clinical practice for haematological malignancies.

Figure A: *target specific drug development cycle*



Dr Grace Gifford, Clinical Research Fellow, St Vincent's Centre for Applied Medical Research and Haematology Registrar, Department of Haematology and Haematopoietic Stem Cell Transplant

Professor David D. Ma, Medical Specialist, St Vincent's Clinic; Director of Research and Clinical Stem Cell laboratory, Department of Haematology and Haematopoietic Stem Cell Transplant; Programme Head, St Vincent's Centre for Applied Medical Research, St Vincent's Hospital Sydney; and Professor of Medicine (Conjoint), the University of New South Wales

1) Acute Promyelocytic Leukaemia – molecularly targeted differentiation therapy

Acute promyelocytic leukaemia (APL) is a biologically unique type of acute myeloid leukaemia (AML) that is highly treatable.

The leukaemic cell is a granulocyte (neutrophil, eosinophil, basophil) precursor called a promyelocyte. Patients are neutropenic as leukaemic promyelocytes fail to mature and leukaemic promyelocyte granules cause life-threatening coagulopathy. Overall long term survival was less than 20% prior to the advent of the new drugs (Table 1).

In APL, the promyelocytes harbour a balanced translocation between chromosomes 15 and 17, fusing the nuclear regulatory factor PML (promyelocyte) and RAR-α (retinoic acid receptor alpha) genes. The PML-RARα fusion transcript interferes with promyelocyte maturation and differentiation.

The history of all-trans-retinoic-acid (ATRA) in APL began in 1980 when *Breitman et al.* discovered the ability of retinoic acid to promote maturation of a leukemic cell line, HL-60. The first reports of the clinical success of oral ATRA in APL came from Shanghai, China in the late 1980s. The next major break-through was the rediscovery of arsenic trioxide (ATO) that can promote maturation and death of leukaemic promyelocytes.

Due to the potentially catastrophic DIC in APL, it is recommended treatment be commenced prior to definitive confirmation of the diagnosis by cytogenetics or polymerase chain reaction (PCR). APL can usually be presumptively diagnosed by considering the clinical presentation, review of the peripheral blood film with or without morphological assessment of the bone marrow for characteristic leukaemic promyelocytes (see Figure B).

ATRA and ATO are the frontline drugs to control DIC and the disease. In conjunction with vigilant blood product support, these new drugs are effective in preventing early deaths due to DIC in APL.

Because of the effectiveness of these new drugs, the use of conventional chemotherapy is mininised to a few doses of anthracyclines during induction therapy reducing the risk of acute and long-term cytotoxic drugs. Induction is followed by consolidation therapy with ATRA and ATO, and then oral maintenance therapy for two years.

An adverse effect of ATRA and ATO is the "differentiation syndrome". Clinically, this presents with cardiac and respiratory distress due to excessive inflammatory response to white cells in the pulmonary vasculature. Management is supportive, including corticosteroids.

Understanding the molecular basis of APL allows the detection of treatment response and early disease relapse at a sub-cellular level by real-time PCR (RT-PCR) in an otherwise well patient with normal full blood counts and coagulation profiles.

The use of ATRA and ATO treatment has drastically improved the lives of APL sufferers. Long term survival exceeds 80-90% and furthermore in our experience, fertility preservation appears to be possible with this new treatment approach.

Table 1: Clinical Presentation of APL

- Usually young
- Bruising and bleeding symptoms
- FBC: severely thrombocytopenic, neutropenic, maybe anaemic
- Coagulation profile: disseminated intravascular coagulation (DIC) with prolonged APTT, PT, low fibrinogen and elevated d-dimer

Table 2: Clinical Presentation of CML

- Often incidental; asymptomatic, high white cell count on FBC, enlarged spleen discovered on physical examination
- Symptoms of hyperviscosity due to high white cell count such as headaches, visual disturbance, priapism (See Figure C)
- Symptoms from high metabolic rate: low grade fever, sweating
- Splenomegaly causing early satiety, left upper quadrant discomfort
- May present in accelerated or blast phase as acute leukaemia

2) Chronic Myelogenous Leukaemia – molecularly targeted tyrosine kinase inhibitor therapy

Chronic myelogenous leukaemia (CML) may present asymptomatically with leucocytosis discovered incidentally, to multi-organ effects of hyperviscosity or

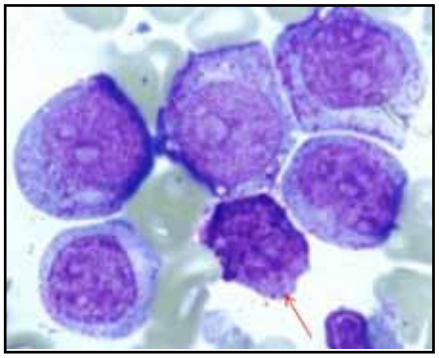


Figure B: *Bone marrow of a patient with APL. Malignant cells are promyelocytes with large nucleus and granules fill the cytoplasm. Auer rods (red arrow) is seen in a cell. Absence of myelocyte maturation is evident.*

Figure C(i) *Hyperviscous blood in CML – this bag of white cells was taken from a CML patient who required apheresis to rapidly reduce white cells. The plasma (top layer) is reduced compared with the markedly increased haematocrit (bottom).*

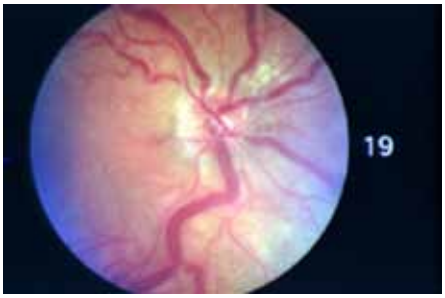


Figure C(ii) *Leucocytosis causing hyperviscosity retinopathy in CML*

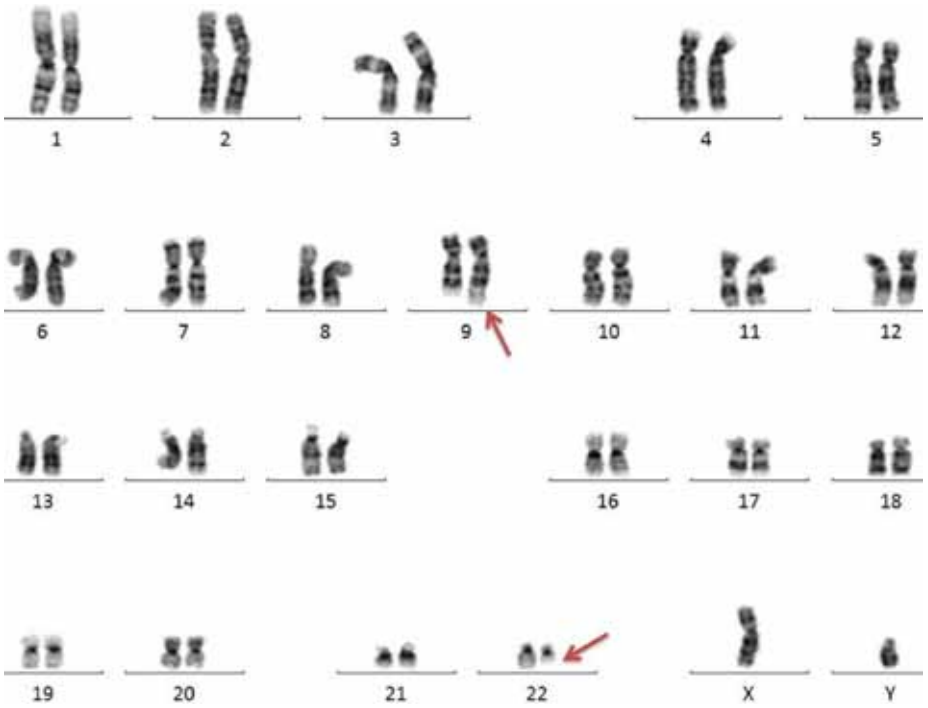


Figure D: *The Philadelphia Chromosome – the karyotype of a CML patient shows translocation of chromosome 22 (shortened) to chromosome 9 (elongated)*

transformation to acute leukaemia (see Table 2). For decades, this disease could only be cured by allogeneic haematopoietic stem cell transplantation which carried significant treatment morbidity and mortality.

Recognition of the characteristic molecular abnormality in CML has revolutionized its treatment and markedly improved outcomes for patients. The Philadelphia chromosome characterizes CML and results from segments of the breakpoint-cluster region *(BCR)* on chromosome 22 and Abelson murine leukemia viral oncogene homolog 1 gene *(ABL1)* on chromosome 9 fusing together (see Figure D). The *BCR-ABL1* fusion gene enhance a cellular enzyme called tyrosine kinase (TK) which normally functions as an "on" or "off" switch in cellular functions. In CML, tyrosine kinase is "on" all the time, promoting cellular pathways so that leukaemic cells proliferate uncontrolledly. *BCR-ABL1* is measured by various techniques, most commonly with RT-PCR that can be performed on the peripheral blood.

Small molecules have been developed to specifically inhibit the TK activity of *BCR-ABL1*. Through overcoming the abnormal *BCR-ABL1* activity, leukemic cells lose their survival advantage. An oral agent, imatinib, a TK inhibitor (TKI) heralded the first successful introduction of targeted molecular therapy in cancer.

Oral TKIs are now the standard of care for CML patients who present in "chronic phase" without increased number of leukaemic blasts. Newer TKIs are available. These differ in effecting disease response, adverse effect profiles and patient tolerability. Major molecular response (MMR) is the goal of treatment, which occurs when leukaemic *BCR-ABL1* transcripts are below the threshold of detection by PCR. The depth and duration of MMR correlates with overall survival and leukaemic transformation. Disease control is conveniently monitored in the peripheral blood by RT-PCR for the *BCR-ABL1* transcript.

Oral TKIs are unlike conventional chemotherapy. They do not cause cytopenias, hair loss, mucositis and fertility is usually maintained. Common adverse effects of TKIs include nausea, diarrhoea, fluid retention and myalgia. These adverse effects can often be managed symptomatically but, otherwise, dosage adjustments or changing to an alternate TKI may be considered.

Adherence to TKIs is vitally important and continual patient education is necessary to prevent loss of disease control.

Areas of uncertainty that are being investigated include patients with stable CML on TKIs who wish to become pregnant and when (or if at all) TKIs may be safely stopped in patients in molecular remission. In our practice, many patients have remained in molecular remission for over a decade and have a good quality of life.

3) Myelodysplastic Syndrome – epigenetic therapy

Myelodysplastic syndrome (MDS) is a clinically and biologically diverse group of clonal haematopoietic stem cell diseases characterized by ineffective haematopoiesis (Figure E) and increased risk of acute myeloid leukaemia. Clinical presentation is shown in Table 3.

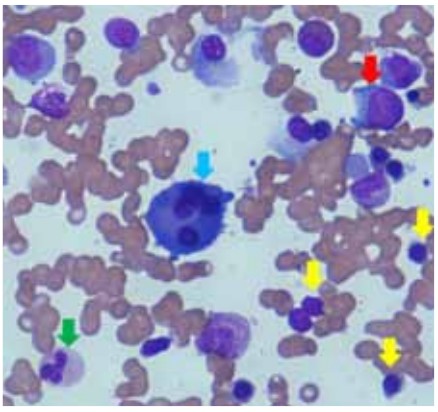


Figure E: *Bone marrow of a patient with MDS – this shows abnormal haematopoiesis in all three cell lineages. The central large cell is a megakaryocyte (blue arrow) which breaks up to form platelets. It shows abnormal nuclear segmentation. A blast (red arrow) is seen, and the neutrophil (green arrow) is hypogranular. Red cell precursors (yellow arrows) show nuclear irregularity and irregular cytoplasm. These abnormal cellular features are typical of ineffective haematopoiesis in MDS.*

The International Prognostic Scoring System (IPSS) for MDS takes into account the karyotype, number of cytopenias (haemoglobin <100g/L, absolute neutrophil count <1.8x109/L, platelets <100x109/L) and percentage of myeloblasts in the bone marrow. Poor prognosticating factors are chromosome 7 abnormalities, 3 or more chromosomal

Table 3: *Clinical Presentation of MDS*

- Usually older patients
- Usually asymptomatic; cytopenias being discovered upon laboratory investigation for other reasons
- Less commonly; symptomatic anaemia; symptomatic neutropenia and/or thrombocytopenia

abnormalities, high myeloblast count and more than one cytopenias. The exact histopathological diagnosis, prognostic features and patient characteristics – age, performance status and psycho-emotional philosophy – affect treatment considerations.

Observation alone may serve many patients with MDS. Treatment is reserved for those who have symptomatic cytopenias or have features that increase the risk of developing leukaemia. In the past, treatment options have been limited to bone marrow transplantation or supportive care and palliation. Transplantation is potentially curative but has significant morbidity and mortality. Furthermore, MDS patients are predominantly elderly and unable to go through the rigors of a transplant. Supportive care includes blood transfusion, haematopoietic growth factors, iron chelation, prevention and early treatment of infections.

Recent advances in medical research have led to the discovery of epigenetic mechanisms of controlling gene expression. DNA methylation is an example of an epigenetic control that has clinical application in haematological malignancies. When DNA methylation occurs in a gene regulatory region, genes in this region are silenced. Aberrant DNA methylation in tumour suppressor and cell-cycle regulatory genes have been observed in MDS, leading to a new target for therapy.

Novel agents include 5-azacitidine and decitabine, which are nucleoside analogues that reverse aberrant DNA methylation and promote re-expression of tumour suppressor genes, leading to cell differentiation. For patients, this means reducing transfusion needs, improved overall survival and prolongation of the time to AML development. These novel drugs are particularly suitable for elderly patients in whom chemotherapy and bone marrow transplantation are impossible. For younger patients, there is emerging evidence that these agents may be used prior to haematopoietic stem cell transplantation as a "bridge" to curative therapy.

Azacitadine is administered by subcutaneous injection for 5-7 days per cycle. No long-term efficacy data is as yet available and oral formulations are being investigated. The common adverse effects of local skin irritation and nausea are usually manageable.

Table 4: *Clinical Presentation of lymphomas*

- Variable presentation due to heterogeneous group of malignancies with variable clinical behaviour and aggressiveness
- Painless enlargement of lymph nodes
- Constitutional (B) symptoms: night sweats, fevers, malaise, anorexia, fatigue

4) B cell malignancies – immunotherapy and risk stratified treatment

Lymphomas and chronic lymphocytic leukaemia (CLL) are malignant diseases of the lymphoreticular cells and are the sixth commonest form of cancer affecting Australians. Lymphomas are divided broadly into Hodgkin's and non-Hodgkin's lymphomas (NHL). The latter is a heterogeneous group which varies considerably in its pathobiology, prognosis and management. NHLs are primarily categorized according to the cell type from which they derive (World Health Organization Classification) as well as clinical features (See Table 4). Around 80-85% of NHLs are derived from B lymphocytes.

The discovery of CD20 (cluster of differentiation, 20) on lymphoid cells heralded a new target for therapy. This cell surface protein is expressed on almost all B-lymphomas and chronic lymphocytic leukaemias, and testing for its presence is part of the normal diagnostic procedure. As CD20 does not occur on early B cells, targeting CD20 should not result in depleting normal B cells in the long term.

Rituximab is a monoclonal antibody that targets CD20 and eliminates B lymphoid cells (including malignant B lymphoid cells) from the body, allowing a new population of normal B cells to develop from haematopoietic stem cells. Rituximab is administered intravenously. Mild infusion adverse effects such as fever, chills and rigors are common. These symptoms are usually manageable and should not lead to omission of Rituximab. As Rituximab also depletes normal mature B-lymphocytes, reactivation of dormant infections may occur. Accordingly, hepatitis serologies and HIV testing should be performed on all patients as well as latent tuberculosis testing for at-risk candidates.

In aggressive B-lymphomas, such as diffuse large B-cell lymphoma, the addition of Rituximab to conventional cytotoxic chemotherapy has improved survival by 20%. In all NHL of B cell type, the addition of Rituximab improves rates of complete remission. An example of response to Rituximab is shown in Figure F. Rituximab has also been shown to be effective as mono- or combination therapy in post-transplant lymphoproliferative disorders. Antibodies to other cellular proteins are in clinical trials for other cancers.

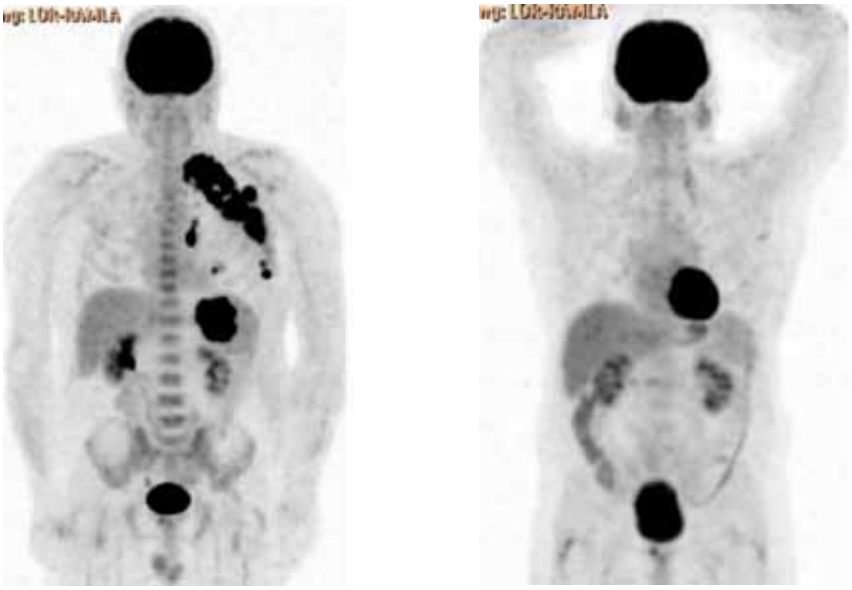


Figure F: *Positron Emmission Topography (PET) images before (left) and after (right) Rituximab containing treatment for a patient with lymphoma. There is physiological uptake of fludeoxyglucose (FDG) in the brain, heart and bladder. Lymphomas are metabolically active and take take up FDG. All lymphoma deposits have disappeared after completion of treatment (right), with only physiological uptake remaining.*

5) Myeloma – immunomodulatory therapy and proteasome inhibition

Myeloma is a bone marrow based, multifocal plasma cell malignancy associated with a monoclonal immunoglobulin protein, a paraprotein. The disease is clinically diverse, from smouldering asymptomatic disease to aggressive forms due to deposition of the paraprotein in organs and tissues (See Table 5). The paraprotein is detectable in blood and/or urine, and biopsy of the bone marrow shows infiltration by clonal plasma cells. Histological examination of lytic bone lesions and focal tumoural masses are also diagnostic (See Figure G). Each year in Australia, about 1000 new cases of myeloma are diagnosed.

Table 5: *Clinical Presentation of Myeloma*

- Usually older patients
- Monoclonal protein (paraprotein) in blood or urine, discovered upon laboratory investigation
- End organ damage: bone marrow failure (particularly anaemia), renal impairment, symptomatic lytic bone lesions (Figure H), hypercalcaemia

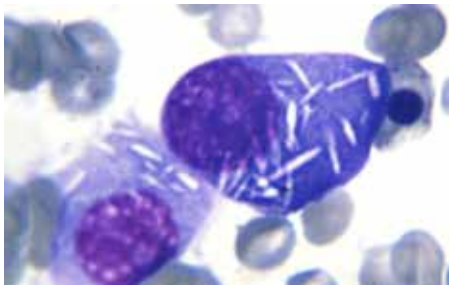


Figure G: *Myeloma cells are malignant plasma cells. Intracellular, needle-like crystalline inclusions maybe seen in myeloma cells due to accumulation of cytoplasmic immunoglobulins secondary to a block in protein pathway.*

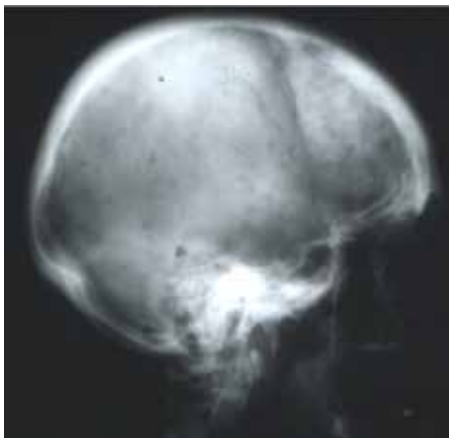


Figure H: *X-Ray of a skull with multiple radiolucent punched out lesions, "pepper pot skull". Myeloma affects both the axial and appendicular skeleton.*

Myeloma remains an incurable disease but with newer treatments there is hope for durable complete remission and long-term disease control.

Immunomodulatory drugs (IMDs) and proteasome inhibitors are novel agents that are now widely used in treating myeloma.

The IMDs induce growth arrest and/or death of myeloma cells. Other effects include making the bone marrow microenvironment unfavourable to myeloma cells, through mechanisms such as inhibiting blood supply and employing natural killer cells to attack myeloma cells.

Thalidomide was the first IMD used in myeloma. Given Thalidomide's history of causing major birth malformations, its safe use is heavily regulated. Thalidomide is taken orally, and common adverse effects are somnolence, constipation and peripheral neuropathy. Lenalidomide is a currently available next generation IMD, approved for patients who fail to respond to thalidomide.

Proteasome inhibitors were developed to counteract the 26S proteasome, an enzyme system that normally breaks down cellular proteins. Dysfunction of the 26S proteasome is one of the causes of myeloma disease progression. Bortezomib is a proteasome inhibitor and it delays tumour growth *in vitro*, prolongs clinical remission and delays disease progression. It is given intravenously or subcutaneously. Common adverse reactions include fever, hypotension, gastrointestinal discomfort and peripheral neuropathy.

Treatment of myeloma is constantly evolving and up-front treatment by cytotoxic chemotherapy is being gradually replaced by these new drugs. While myeloma remains incurable, novel agents may maximize control of this malignancy.

Conclusion

Progress in our understanding of the pathological processes in haematological malignancies at the molecular level has translated to improve patients' livelihood and in most cases survival through novel diagnostic, prognostic and therapeutic means. Effective, new agents (summarized in Table 6) have become new standards of care in APL, CML, MDS, lymphomas and myeloma. It is envisaged that novel target specific drugs and immunotherapy will continue to advance the management of patients suffering from these cancers, replacing the need for traditional cytotoxic chemotherapy.

Table 6: *non-chemotherapy agents used in haematological malignancies*

Condition	Novel non-cytotoxic therapy as standard of care	Comments
APL	All-trans-retinoic acid and Arsenic Trioxide	High response rate and >80-90% overall survival
CML	Tyrosine kinase inhibitors	Excellent High response rate and > 90% overall survival.
MDS	Hypomethylating agents	Delays progression to leukaemia, improves QOL and survival
B-lymphoid malignancies	Rituximab (immunotherapy – chimeric antibody)	Improves response rate and overall survival in lymphomas and CLL by 20%
Myeloma	Immunomodulatory Drugs and Proteasome inhibitors	Improve disease response; 10 year survival increase from 25% to over 40%

Sr. M. John Baptist De Lacy, Dr James Robertson and the 'Bible Incident' Revisited

Dr Maxwell Coleman

Prelude:

Dr Maxwell Coleman has for some time been meticulously researching the history, particularly the surgical history, of St. Vincent's Hospital and this article is an excerpt from that research. It provides insight into the early establishment and the central characters of the time.

The Story:

Much has been written about the controversial so called 'Bible Incident' at St Vincent's Hospital in 1859. However there may have been other forces at play that led to the resignations of the Mother Superior, Sr. M. De Lacy and the Hospital's first Surgeon, Dr James Robertson?

By the year 1853, of the original five sisters who arrived in Sydney's Campbell Cove on 31 December 1838, Sr. M. De Lacy was the only one in Sydney and the only one with nursing training. The congregation numbered 10 but the influenza epidemic caused the deaths of three of these sisters.

A fund raising appeal was instituted in August 1853 to provide a residence for the Sisters and a Free Hospital "*open to people of all religions*" to enable them to fulfil their mission of looking after the sick poor. This had the support of Archbishop Polding.

On 17 January 1855, Governor Fitzroy issued a deed of grant on a small parcel of Crown land near Darlinghurst Goal to be given to the Trustees of the Sisters of Charity for the purpose of their residence and Hospital. The Trustees were Sr M. John Baptist De Lacy (then the Mother Superior), John Hubert Plunkett (Attorney-General of New South Wales) and Sir Charles Nicholson (Speaker of the Legislative Assembly and Chancellor of the University of Sydney). Dean McEncroe, Acting Vicar-General and a strong supporter of the Sisters, represented the Church in the negotiations.

The block of land being long and narrow was not immediately suitable for the construction of a Hospital. As an interim measure *Tarmons*, at Woolloomooloo Heights (Potts Points), was offered by Sir Charles Nicholson to the Sisters of Charity for the enormous sum of £10,000. Sir Charles generously gave £1,000 towards the purchase price. The Sisters received the strong financial support of the local community (regardless of denomination) based on their reputation for care of the sick, poor and marginalised members of society.

The sisters took possession of *Tarmons* on 6 March 1856. Significant repairs were required before it could be used as a hospital. The Hospital was placed under the control of Sr M De Lacy. The other Sisters at *Tarmons* were: the biological sisters Sister M Joseph O'Brien and Sister M Veronica O'Brien; a domestic, Sister Agnes Shortal; Sister Aloysius Raymond, a novice; and the postulants Sister Alphonsus Unsworth (an American) and Sister Xavier Cunningham (the first Australian born to enter the order).

The highly qualified James Robertson (MD University of St. Andrews; MB London University; and Licentiate of the Society of Apothecaries), an Anglican, was duly appointed first medical practitioner to St Vincent's Hospital by the Sisters themselves because the "*institution was for all denominations and was not a Catholic institution*". Similarly, at St. Vincent's Dublin under Mother Mary Aikenhead, protestant ministers were able to attend to patients who were members of their own congregation.

Dr Maxwell Coleman
MB BS (Syd Uni), FRACS, FRCS
Trustee, St Vincent's Clinic Foundation

St Vincent's Tarmons, circa 1860 ... courtesy St Vincent's and Mater Health Services Archives

There had been no dissent at the appointment of the Robertson although Polding later corresponded to Bishop Gould that Robertson's appointment was *"contrary to my judgement, but in deference to Mrs De Lacy."*

By 5 December 1857, fifty patients were attending the house for "*medical advice and relief*" and a ten bed female ward had been fitted out of which five beds were already occupied. On 5 April 1858, a 10 bed male ward was opened.[1]

Unfortunately, over time there were increasing tensions between Sr De Lacy and the hierarchy. At a visitation from 4 to 7 November 1857, Polding presided over an "election" of the Sisters that placed Sr Scholastica Gibbons over De Lacy in management of the Hospital.

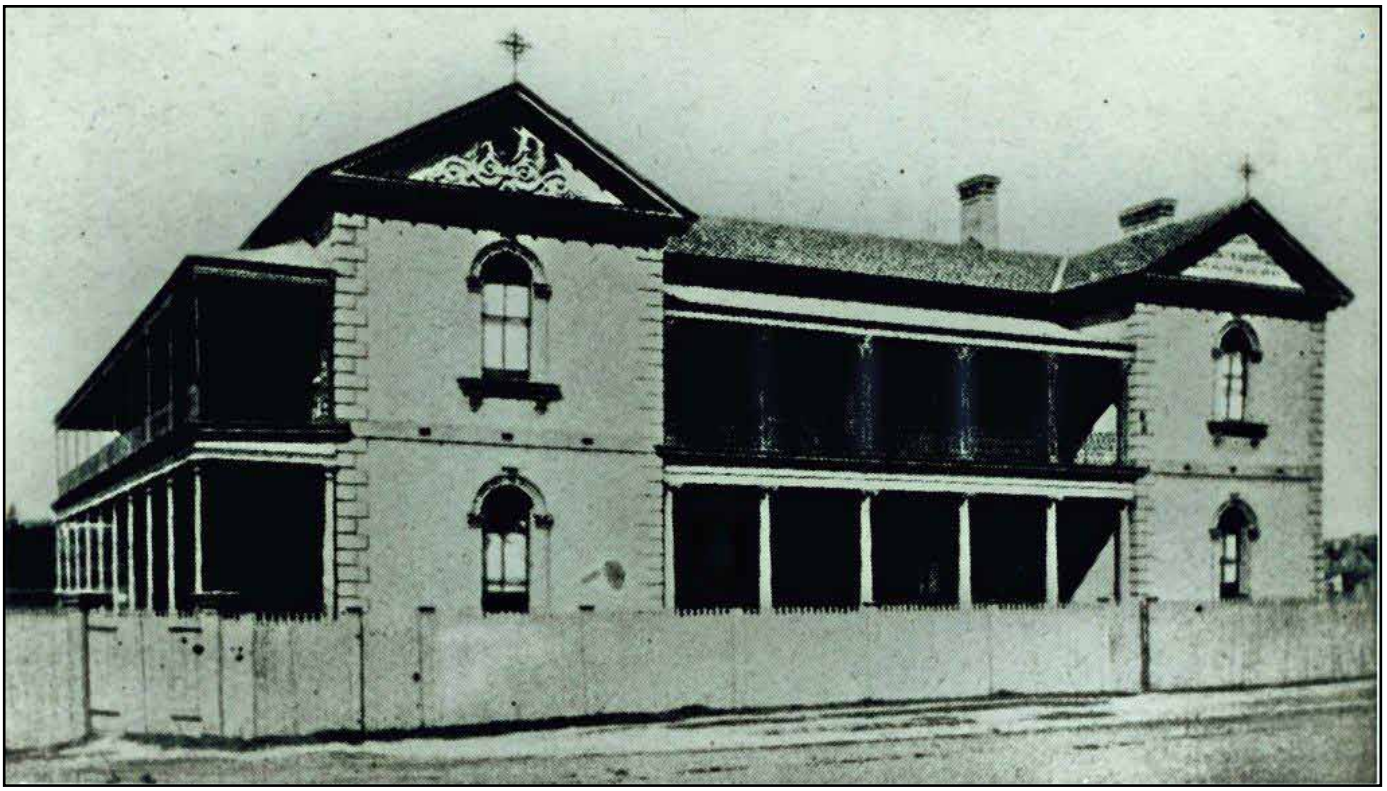
At around this time there were two "trivial" incidents involving Dr Robertson and Sr De Lacy.

The first of these involved a decision to use tank water for patients without the permission of the whole sisterhood. "..Sr Gibbons convened a meeting of the senior sisters (De Lacy and the O'Brien sisters) in the chapel. She appointed Mother Mary Joseph O'Brien "Rectress of this Convent" but left De Lacy in charge of the Hospital with the intolerable rider "*but all matters are to be communicated to me, of which I will inform the Archbishop who will always decide for us.*"

The second incident was the situation surrounding Miss Gray documented in the writings of Archbishop Polding and Mother M. Scholastica Gibbons. Miss Gray was a novitiate (originally instructed and received into the Church by Abbot Gregory) who *had reached the term of her novitiate and was to be either professed or dismissed. At the time, her non-theological duties (as approved by Sr De Lacy) were to assist Dr Robertson in the dispensary each day. At the instruction of Dr Robertson, she would make up the prescriptions and generally "attend to him." It became the view of Sr Gibbons that Miss Gray began to "neglect or omit her own spiritual duties under the pretext of duties in the Hospital". Ultimately, the unfortunate Miss Gray renounced her holy state, was taken by Robertson to his own house, paraded through Sydney in his carriage and accompanied him and his lady to the Protestant Church - and is now a declared Protestant."*

On 16 May 1859, an incident occurred which was to bring all tensions to breaking point. Reverend Patrick Kenyon, a Catholic curate from the Sacred Heart Presbytery on Darlinghurst Hill, was visiting patients in the female ward when he noted on a mantle shelf above a fireplace "*Protestant prayer books and bibles having 'St Vincent's Hospital' and nothing else written on the fly leaves.*" He then took a Prayer Book and Bible into the adjacent surgery and called for Sr De Lacy. He told her "*it was not lawful for her and her sisters to supply these books and that if (he) should find they continued to do so (he) would feel obliged to bring the matter under the notice of the Archbishop.*"

The incident triggered a cascade of events. De Lacy informed Dr Robertson about Rev. Kenyon's action. Dr Robertson went to Archbishop Polding who made the following determination:"*after conversing, His Grace instructed me (Robertson) to direct one of the Sisters (De Lacy) to inform Mr Kenyon, on his next visit to the Hospital, that he must not interfere in the Management of the Hospital, that of course he could visit the Sick &c., but that he was in no wise to interfere in other matters, and that the books in question were not again to be removed from the Ward."* In a letter to the Editor of the *Sydney Morning Herald* written on June 3rd and published on 7 June 1859 explaining and defending his actions, Kenyon was clearly sorry. He stated that whilst at no time was he "*disabused*" of his assumption that the sisterhood had supplied the Books, he went on to further explain his views "*.. all patients in the hospital, admitted into it irrespectively of their faith, and solely because they were sick and poor, might have, by all means their own books to use, might have their own ministers sent for at their request, to be their comforting friends..*" He apologised: *"if I erred in thinking those books were theirs (the Sister's), I am sorry for it, as men are sorry for an accident. I am more sorry for it, because of the great sorrow*



St Vincent's circa 1887 ... courtesy St Vincent's and Mater Health Services Archives

and misery that have grown up along side of my act." One is left with little doubt as to his opinion of the sisters - *"..they should be known … in their true character of kindliest best nurses, 'but little lower than the angels in their loving kindness and gentle charity"*.In the end, De Lacy's position was deemed untenable and she decided to return to Ireland. Dr Robertson (a loyal supporter) provided her fare and subsequently her supporters in the colony raised a subscription to give her a departing gift.

The timeline here is of interest in that De Lacy announced her resignation on 26 May 1859 and departed the Colony on 2 June 1859. Robertson submitted his resignation to Polding on 18 May, two days after the "bible incident". Doubtless he would have been only too aware of the tensions with the Catholic hierarchy and within the congregation of the Sisters of Charity. Robertson had worked closely with De Lacy and although Plunkett had been appointed Treasurer of the Hospital it was Robertson, on behalf of De Lacy, who signed off on the first financial report to the Subscribers published in the *Sydney Morning Herald*. It would seem likely that De Lacy may have already flagged her intention to resign to Robertson by 18 May although it was not formally announced until 26 May when she left the Hospital and moved in with the Plunketts at their home in Macquarie Street, Sydney.

Dr Robertson addressed a letter to the Subscribers to the Sydney Infirmary and Dispensary written on 9 June that appeared in the *Sydney Morning Herald* on 10 June 1859. In this he applied for the position of Surgeon to the Sydney Infirmary (also encompassing membership of the Board of Examiners of the Medical Faculty of the University of Sydney) to replace Dr Donald Macintosh McEwan following his death on 24 May. He had been Honorary Surgeon at the Sydney Infirmary since 1847.

The Sydney Infirmary at that time was in negotiation with the University of Sydney about the establishment of a Medical School and it is plausible that Robertson may have taken this opportunity to change institutions to be more involved with the Medical School

A further reason for leaving may have related to his desire to practice as a surgeon. The facilities at *Tarmons* to operate were limited.

The "silence" in the newspapers concerning Dr Robertson's resignation even though by all accounts he was a conscientious, well regarded and of considerable ability might indicate that the reasons were generally "known". Although there was broad coverage in the *Freeman's Journal*, subsequently reported in the *Sydney Morning Herald* on 2 June 1859, of a meeting called by members of the Catholic community in support of Sr De Lacy who had recently resigned and despite a long and detailed speech by John Plunkett analysing the reasons for her departure, there was but a mention of Robertson's resignation.

It is also in keeping with Dr Frederick Milford's letter to the Editor in the *Sydney Morning Herald* [12 August 1869] in reply to a letter by Dr John Dunmore Lang who had questioned the Hospital's tolerance of Protestants citing Dr Robertson's resignation and the "bible incident":

"Sir,- When I succeeded the late lamented Dr Robertson as Surgeon to St Vincent's Hospital, he told me that the reason of his resignation had nothing to do with religious motives…"

It is the thesis of this communication that the 'Bible Incident' was but one of the triggers that lead to the resignations of Sr De Lacy and Dr Robertson and not the cause. Sr De Lacy returned to Ireland and lived out her life as a Sister of Charity. Robertson died on 17 December 1862, aged 40 years, of tuberculosis at *Woodside* near Parramatta.

Optimising weight as a medical intervention in chronic disease: an opportunity for better health and quality of life

Prof Katherine Samaras
Dr Jonathan Paetzholdt

Introduction

Obesity has reached epidemic proportions in much of the industrialized world with 60% of adults classified as overweight or obese. For the individual, obesity impacts on aspects of daily living and long-term health outcomes. Obesity plays a significant role in the development of numerous diseases including cardiovascular disease, type 2 diabetes mellitus, hypertension, obstructive sleep apnoea, gastro-oesophageal reflux disease, depression and osteoarthritis. Obesity is costly in terms of health, sick leave and premature loss of workforce. Obesity was estimated to cost $2 billion in health costs alone in 2008 and twice that in lost productivity.

In the overweight and obese, weight reduction (even a modest 5-6 kg loss) has immense health benefits. Over the last 4 years, in a Campus-wide research effort involving the Departments of Endocrinology, Cardiology, Upper Gastrointestinal Surgery and the Garvan Institute of Medical Research and supported by a St Vincent's Private Hospital Ladies' Committee Sister Bernice Grant, our research team has shown that a 6kg weight loss induces rapid improvements in diabetes,[1] arterial stiffness[2] and inflammation.[3] Our research has characterised how obesity promotes immune cell-induced inflammation and how this negatively impacts metabolism and physical health. Further, we have shown that weight loss reverses immune system dysregulation and inflammation.[3] Our findings build on long-term studies which show that sustained weight loss in the obese reduces the 10-year incidence of diabetes (by 95%), heart disease (by 50%) and cancer (by 60%). Clearly, assisting obese people to lose weight and maintain a lower weight is an important component of physical health in chronic disease management. This paper elaborates on strategies for weight reduction for three important chronic disease areas served on the St Vincent's Campus, specifically chronic heart failure, diabetes and mental health.

Weight reduction and heart failure

St Vincent's has an international reputation for its excellence in management of heart disease, heart failure and for heart transplantation. Obesity promotes heart disease by increasing cardiac load, through effects on blood volume, heart rate and left ventricular loading. Obesity also contributes to heart risk factors including blood pressure, hyperlipidemia, diabetes, insulin resistance and sleep apnoea. Obese patients with heart failure have significantly greater morbidity and mortality compared to those with healthy weight.[4]

Weight loss induces multiple cardiovascular benefits in the obese, including improved cardiac remodelling, lower blood pressure and improved lipids and glucose tolerance. Weight loss, either through lifestyle intervention and/or bariatric surgery, has beneficial effects on the health of people with severe heart failure, improving left ventricular ejection fraction and exercise tolerance and reducing the need for diuretic therapy.

Heart failure patients undertaking weight loss require medical supervision with attention to electrolytes and titration of diuretic therapy, as rapid electrolyte shifts can occur.

The St Vincent's Campus has two designated services for the management of obesity: the Australian Centre for Metabolic Health (St Vincent's Clinic) and the Obesity Clinic (St Vincent's Hospital). Both serve the needs of obese patients referred from the Department of Cardiology and the Heart Transplant Unit to optimise weight and cardiac function. We recently reported the benefits of weight loss in two patients with severe heart failure who required heart transplantation.[5] Obesity is a contra-indication to transplantation as outcomes are poor, thus both patients were denied access to transplantation. Both patients underwent bariatric surgery with support from the expert anaesthetic and intensive care teams at St Vincent's. Both patients received ongoing nutritional support and lost significant amounts of weight. In one case, weight loss improved heart failure symptoms to such a degree that heart transplantation was no longer required. In the other case, the weight loss achieved permitted the patient to qualify for transplantation

Professor Katherine Samaras MBBS, PhD, FRACP
Senior Staff Specialist in Endocrinology, St Vincent's Hospital, Consultant Physician in Endocrinology and Metabolism, St Vincent's Clinic, Co-director, Australian Centre for Metabolic Health, St Vincent's Clinic

Dr Jonathan Paetzholdt, MBBS, Dip Obstet (RACOG), FRACGP
Co-director, Australian Centre for Metabolic Health, St Vincent's Clinic

which was successfully undertaken. Both patents are now engaged in full-time work and are no longer disabled by their cardiac disease.

Weight reduction and diabetes

Type 2 diabetes is a common disease affecting 7% of the adult Australian population and almost 1 in 4 people aged over 70 years. It is the commonest cause of renal failure and blindness in Australia. Many people with diabetes are overweight or obese. Further, some important and commonly used anti-diabetic medications promote weight gain, including sulfonylurea, thiazoledinediones and insulin. Thus, weight management is part of benchmarked diabetes care. Obesity deteriorates control of glucose, lipid and blood pressure. Higher rates of cancer are also found in people with diabetes and this is considered to be due to excess weight.

Modest weight loss improves most aspects of diabetes. Caloric restriction acutely reduces blood glucose levels, with benefits evident within three days. Weight loss will improve insulin sensitivity, evident within two weeks. These effects are considered to be due to reduced triglycerides within the liver and muscle, which rapidly improves the effectiveness of insulin. There is also increasing evidence that nutrient excess promotes inflammation which interferes with insulin action and worsens insulin resistance. Further, nutrient-induced inflammation is also implicated in the beta-cell dysfunction that characterises diabetes and results in impaired insulin secretion. Any means of chronically reducing caloric intake will improve glucose levels and insulin resistance in diabetes, as well as improving blood pressure and hyperlipidaemia. Unfortunately for many obese people with diabetes, despite best efforts and intentions, they are unable to sustain chronic caloric restriction to the degree to maintain long term-weight reduction. In these circumstances, particularly where diabetes control is poor and places the individual at risk of diabetic complications, bariatric surgery is a therapeutic option.

Weight loss by bariatric surgery in diabetes has been shown to be superior in achieving diabetes remission or optimising glucose control over standard medical intervention, with up to two years follow-up. Selecting the appropriate patient and time for surgery has been debated and it appears that it is never too early or late to intervene with bariatric surgery for weight reduction in diabetes where patients have been unable to make a sustained weight reduction. Beneficial effects in diabetes control and cardiovascular risk factors are evident regardless of diabetes duration or complexity of medication regimens or need for insulin therapy.[6]

Again, the St Vincent's Campus has a long tradition of excellence in diabetes care and research. As one small component of the diabetes services available on campus, our bariatric program (in collaboration with upper gastrointestinal surgeons) serves those patients who, despite concerted efforts at lifestyle change, are unable to achieve or maintain a healthier weight. Our research efforts have shown that bariatric surgery normalises glucose tolerance within two weeks of surgery in 70% of obese people with diabetes. Our research has also highlighted that immune cell-mediated inflammation appears to play a role in this recovery. For example, we found that the degree of improvement in glucose levels in diabetes was related to the reduction of circulating pro-inflammatory immune cells, particularly T-lymphocytes.[1] We also found a 25% improvement in arterial stiffness in obese people with diabetes with weight reduction. Again, links to immune cell-mediated inflammation were found. The improvement in arterial stiffness was related to the reduction of immune cell-mediated inflammation, which we characterised by cell surface expression of activation on monocyte and T-lymphocyte expression of the interleukin-2 receptor which promotes monocyte migration into the arterial wall.

Weight reduction and mental health

People with major mental illnesses have a 20-year shortfall in life expectancy, predominantly due to cardiovascular disease and diabetes. Higher cancer rates are also reported. In part, this excess burden of disease is due to lower rates of health service engagement, late presentation but also recognised under-treatment.

Some drugs used to treat major mental illness can cause weight gain. They include antidepressants, anticonvulsants used as mood stabilising medications and, in particular, antipsychotics. Some antipsychotics can cause very significant weight gain with associated deterioration of blood glucose and lipid profiles. Antipsychotic use is associated with a three-fold increased risk of diabetes which becomes apparent within the first year of use.[7] It is likely that studies quantifying diabetes risk have substantially under-estimated the real risk, since widespread diabetes screening is not yet the standard of care.[8]

Strategies to improve the physical health outcomes of people with severe mental illness include screening and monitoring for metabolic complications with treatment of cardiometabolic risk factors. Initiatives formulated in a collaboration between the Australian Centre for Metabolic Health in St Vincent's Clinic and Dr Jackie Curtis (at the Bondi Centre, Eastern Suburbs Mental Health Programme) promote early intervention for weight maintenance and prevention of weight gain. The program consists of individualised lifestyle counselling with support and follow-up with input from psychiatrists, endocrinologists, general practitioners, dietitians, exercise physiologists, mental health nurses and carers. The program is described in detail elsewhere.[9]

One of the resources from our initiative is the metabolic monitoring algorithm "Don't just screen, Intervene" (www.heti.nsw.gov.au/cmalgorithm), which has been adopted by NSW Health (Figure 1). An adaption of the algorithm has been incorporated into the National Institute for Clinical Excellence (NICE, UK) Clinical Guidelines for management of psychosis in youth (www.guidance.nice.org.uk/CG155/InterventionFramework).

Another important resource from the local collaboration is the HeAL Declaration (Healthy Active Lives for youth with severe mental illness (www.iphys.org.au/HeAL). The Declaration mandates early intervention to preserve physical health in youth with severe mental illness to prevent weight gain, obesity and increased risk for cardiometabolic disease. The Declaration was formally adopted by the NSW Government in September 2013 and was launched internationally in October 2013 in Belgium at a specific meeting, EuroHeAL.

Health policy aside, each overweight or obese individual with severe mental illness requires careful physical health monitoring with effective intervention. Ideally, exposure to weight promoting medication should be minimised however this is not always possible. Lifestyle

counselling of the individual and (where relevant) their families or carers is essential, addressing potential barriers such as knowledge and skills in shopping, food preparation, cooking and budgeting skills. Sedentariness requires specific attention with a graduated physical activity program and diversional therapy, particularly as many of the medications used in the treatment of severe mental illness are sedating. Occupational rehabilitation is an important component of re-engagement with the community and the return to whole health.

A further therapeutic strategy is potential use of the anti-diabetic medication metformin. There are now several randomised controlled trials demonstrating that lifestyle intervention with metformin are superior to placebo for weight management and metabolic health in antipsychotic-associated obesity, or to offset weight gain associated with antipsychotic initiation.[10] Further research is required to determine the best strategies to prevent the cardiometabolic complications of medications commonly used to treat people with severe mental illness. Premature cardiovascular disease and diabetes are the main causes of death in people with severe mental illness and account for much of the 20-year shortfall in life expectancy. Preventive health strategies and early intervention are essential until complication-free medications are developed which should be a mental health priority.

Summary

Effective strategies for management of obesity are important in the management of common chronic diseases and can influence the outcomes of those diseases. Multidisciplinary treatment supporting lifestyle change for weight loss unite the strengths of medical practitioners and allied health professionals to help our patients achieve the best possible health.

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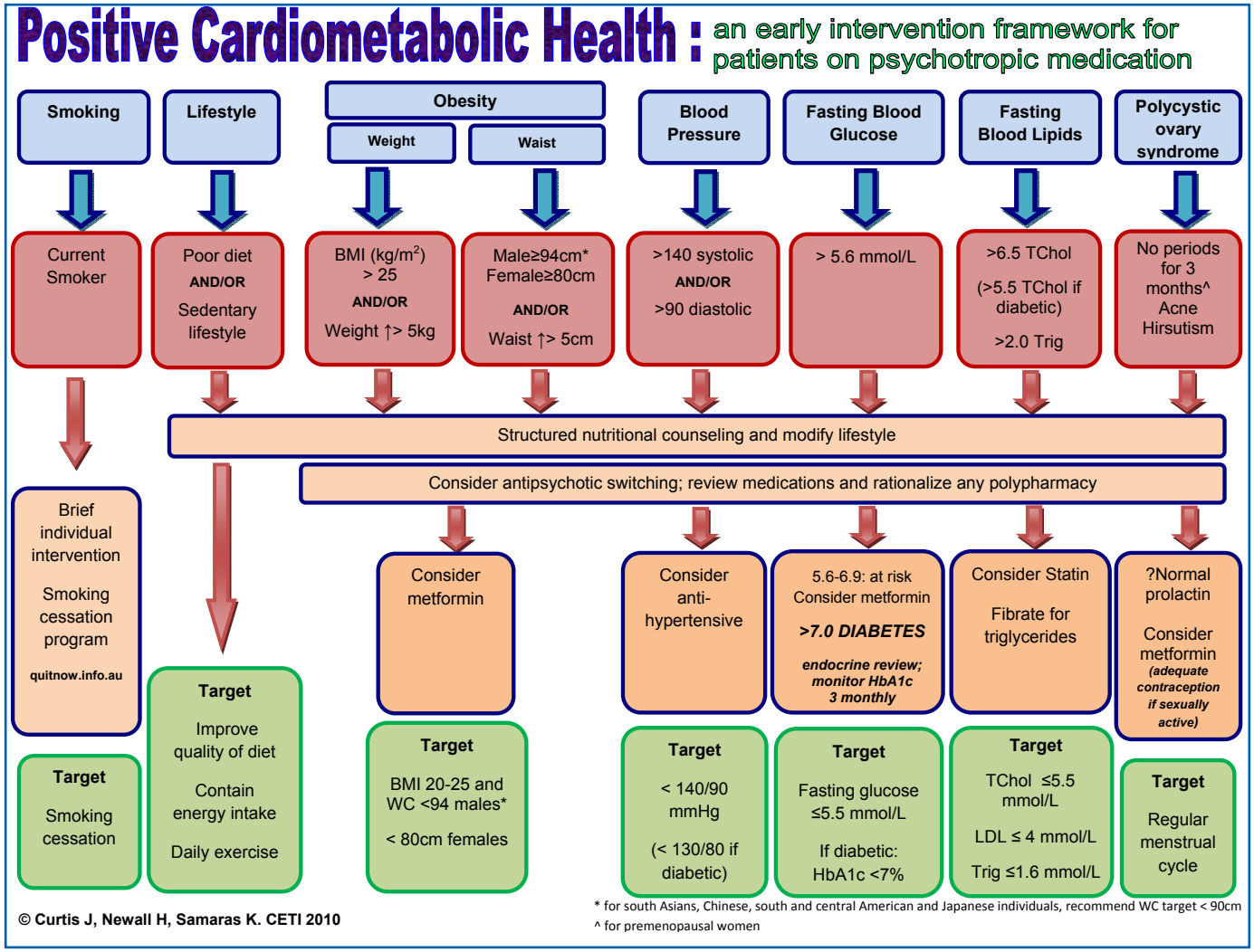


Figure 1: *The metabolic monitoring algorithm*

Non-atherosclerotic causes of External Iliac artery stenosis

Ms Debbie Hamilton
Dr M. A. McGrath

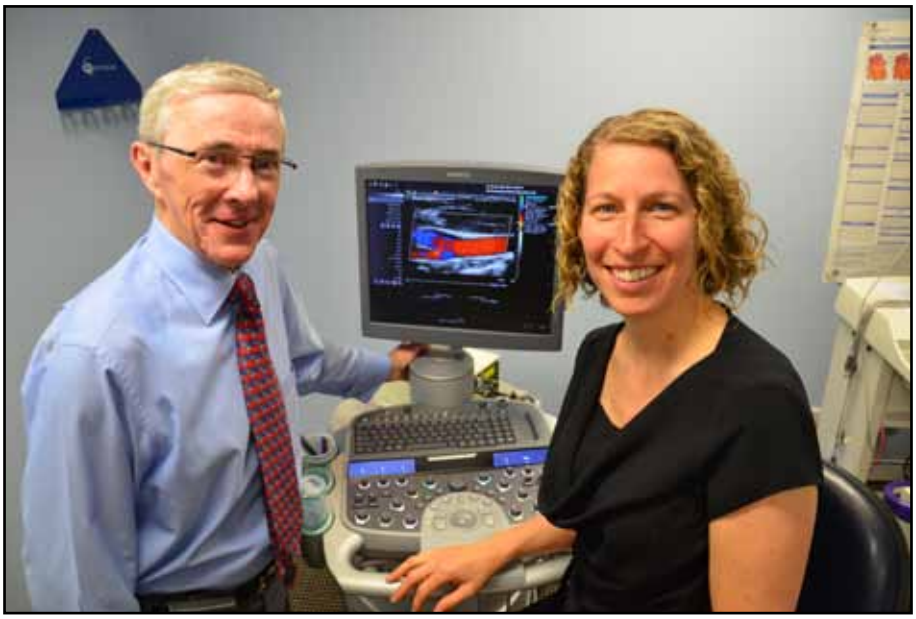
Introduction

The vast majority (over 90%) of arterial occlusive disease is atherosclerotic in nature. This applies throughout the vascular tree and is equally applicable to the External Iliac artery (EIA). However we have identified many other pathologies in this vessel, some of which are specific to the EIA and some of which can be seen in other visceral or peripheral arteries. We have found vascular ultrasound to be a valuable tool in the assessment and follow up of these non-standard cases.

Vascular ultrasound is ideally placed for first line imaging of these patients. Not only is ultrasound non invasive, it is also able to image not just the lumen of the vessel but the characteristics of any luminal obstruction, as well as details of the arterial wall.

Patients with Iliac artery disease of any cause will most likely present with claudication. This intermittent pain results because although the reduced circulation is sufficient to meet the lower limb oxygen requirements at rest, there is an inability to accommodate the 5-10 fold increase in blood flow requirements during exercise. However, the predisposing factors for atherosclerotic disease (increasing age, hypertension, hypercholesterolemia, smoking and diabetes), will generally not be useful indicators for identifying patients in our cohort of non-atherosclerotic cases. In fact, we have found some of these disease processes are most commonly found in young healthy athletes in whom musculoskeletal causes of exercise-induced lower limb pain might otherwise be considered as the initial diagnosis.

The pathologies we have encountered include fibromuscular dysplasia, intimal hyperplasia, dissection, thrombosis, endofibrosis, arteritis, aneurysmal disease, ergotism and cystic adventitial disease. A brief outline of a selection of these patients is included below.



Ergotism

A 39 year old woman presented with a 12 month history of claudication. Both Femoral pulses were reduced and bruits were audible in both groins. She gave a long history of migraines, for which she was taking caffeine-ergotamine tartrate (Cafergot). B-mode scanning demonstrated bilateral hypoechoic circumferential wall thickening of the External Iliac arteries, resulting in a significant lumen reduction of 4mm (Figure 1), confirmed with colour duplex (Figure 2a). The degree of narrowing of an artery is calculated quantitatively based on the velocity measurement, using the concept that as a vessel narrows (at a stenosis), so the blood flow velocity must increase. The velocity of 3.4m/sec was detected, indicating a >50% stenosis (Figure 3). The adjacent arteries were normal. CT angiogram confirmed the findings.

The diagnosis of ergotism was made, a vasoconstrictive reaction to the ergot containing medication. At follow up duplex 1 month post cessation of medication, the wall thickening had reduced significantly, with the lumen now increased to 7mm, and the velocities now decreased to 2.3m/sec, indicating the stenosis was reduced to <50% (Figure 2b). Clinically there was a marked improvement in symptoms. A subsequent follow up at 12 months was normal, with complete resolution of the External Iliac vasoconstriction, a lumen diameter of 8mm and a velocity of 1.6m/sec.

Ms Debbie Hamilton BSc, DMU, AMS
Vascular Laboratory, St Vincent's Clinic
Dr M A McGrath MD, FRACP
Vascular Physician, St Vincent's Clinic

Thrombosis

A 69 year old woman presented with a 2 week history of sudden onset pain and coldness of her left leg. Duplex scanning revealed an occluded EIA, with no evidence of significant disease in the remainder of the lower limb arteries. The appearance of the lumen was hypoechoic (atypical for atherosclerosis) and likely to represent a thrombus or embolus. Further testing failed to identify a cause of the thrombosis or embolism. The Ankle Brachial Index (ABI) was significantly reduced at 0.55 (normal of 1). The patient commenced on Clexane (low molecular weight heparin) and at follow up ultrasound 6 weeks after commencing treatment there was evidence of some recannalisation of the vessel, although significant thrombus was still evident (Figure 4). The ABI had improved to 0.68.

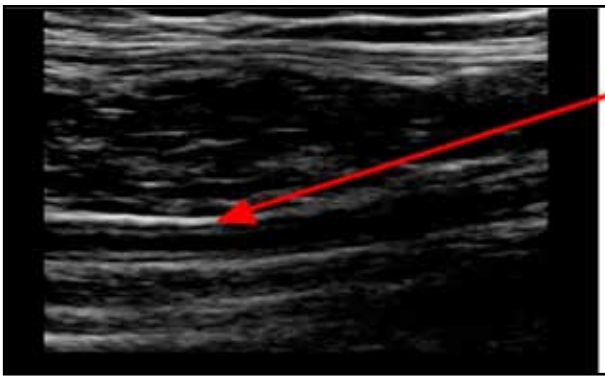


Figure 1: *Ergotism:B-mode imaging demonstrates intimal thickening of the EIA (parallel grey lines within the bright white lines of the adventitia).*

Figure 2a: *Ergotism: Colour duplex of the EIA demonstrating a reduced lumen of 3.5mm on presentation.*

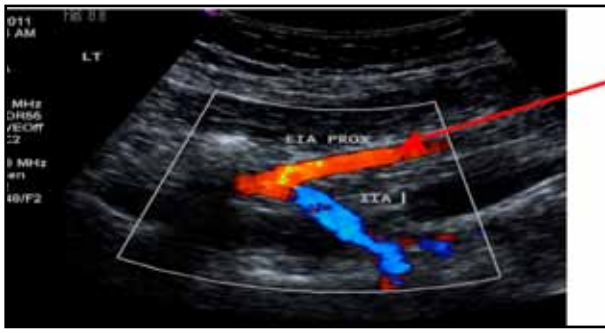


Figure 2b: *Ergotism: Colour duplex of the EIA in the same patient 3 weeks after treatment, demonstrating a lumen size of 7mm (note the calibre change of the EIA compared to figure 2a).*

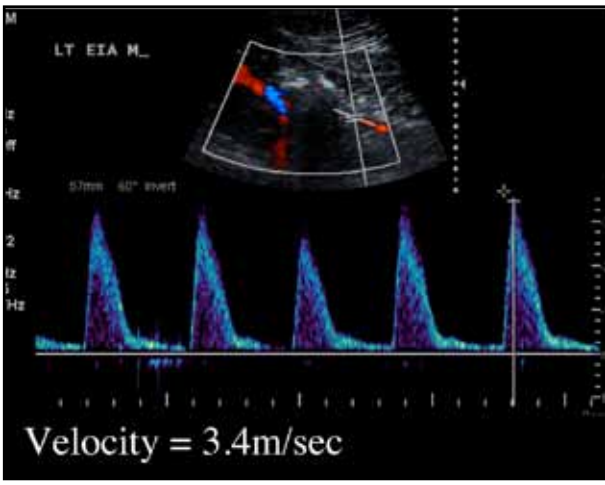


Figure 3: *Ergotism: Spectral waveform demonstrating abnormally increased velocities (3.4m/sec) confirming an arterial stenosis.*

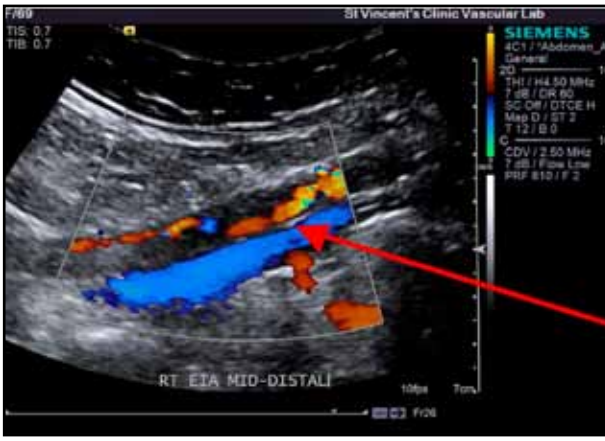


Figure 4: *Thrombosis: Colour duplex demonstrating minor recanalisation of an occluded EIA (a thin channel of colour filling with moderate areas of hypoechoic 'black' regions remaining, representing filling defects indicating residual thrombus).*

Fibromuscular dysplasia

A 57 year old woman presented with pulse synchronous tinnitus. Bruits were noted over the upper cervical segments of the Internal Carotid arteries bilaterally, as well as bruits over the upper and lower abdomen. The patient had no classical risk factors for atherosclerosis. Duplex scanning identified fibromuscular dysplasia (FMD) of the Vertebral, Renal and External Iliac arteries bilaterally. Duplex imaging demonstrated the commonly described 'string of beads' appearance of the External Iliac arteries (Figure 5), with alternate stenoses and dilated segments; wall irregularities were noted, together with flow eddies around the dilated segments (Figure 6), and increased velocities in the stenotic regions.

FMD, which is confined to medium sized arteries, is most commonly found in the Renal and Carotid arteries, however we have had several cases, such as the one above, where FMD has been identified in the External Iliac arteries.

Endofibrosis

A 41 year old professional male cyclist presented with symptoms of right leg claudication during cycling, which came on after only a few minutes of cycling and was alleviated with rest. An exercise study documented a normal ABI at rest of 1.18, but a significantly reduced post exercise ABI of 0.47, with an accompanying abdominal bruit noted. Intimal thickening of the EIA was noted on the duplex scan causing a <50% stenosis (Figures 7 and 8), which increased in severity to a 50-75% stenosis when the patient flexed his thigh to mimic a cycling position (Figures 9 and 10). Digital Subtraction Angiography confirmed the findings, the patient then proceeded to surgery for a patch angioplasty (using Long Saphenous vein) of the EIA. Pathology of the EIA confirmed the diagnosis of endofibrosis.

A disease of incomplete understanding, endofibrosis affects elite athletes, especially but not exclusively cyclists. The symptoms are similar to atherosclerotic disease – claudication and powerlessness, worsening with increasing exercise, leading to reduced exercise

capacity, which is a source of great frustration for the elite athlete. Many of these patients have been to multiple specialists over a long period of time and have had various procedures performed to attempt to alleviate the symptoms, including Popliteal entrapment release and calf compartment decompression surgeries. Imaging studies, notably duplex scanning, reveal thickening of the arterial wall, with resultant stenosis. The damage to the artery may be caused by high frequency repetitive motion during exercise, particularly the cycling motion of hip flexion while bent forward, resulting in localised trauma to the artery, over time leading to intimal thickening and smooth-muscle-cell hypertrophy.

Summary

Various arterial pathologies can be encountered in the Iliac system. The vascular laboratory is a valid and productive first line investigation in the diagnosis and follow up of unusual arterial diseases.

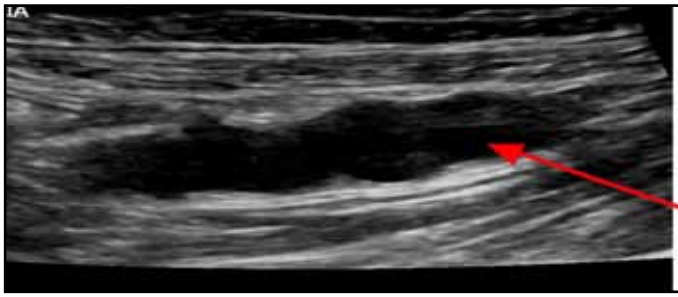


Figure 5: *Fibromuscular dysplasia: B-mode image demonstrating 'string of beads' appearance.*

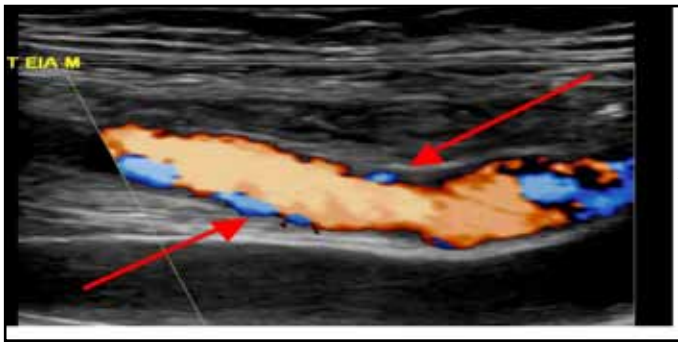


Figure 6: *Fibromuscular dysplasia: Colour duplex image demonstrating flow eddies (blue) into the small focally dilated 'beaded' segments.*

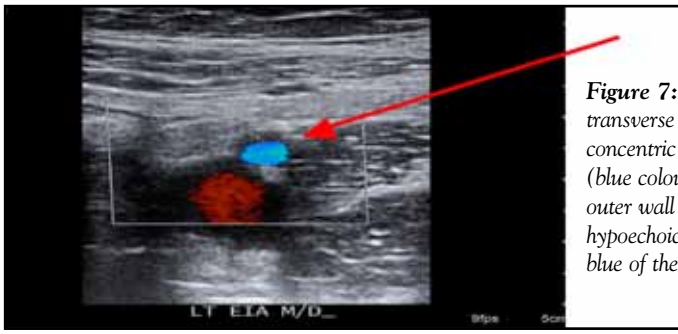


Figure 7: *Endofibrosis: Colour transverse image demonstrating concentric filling defect of the EIA (blue colour does not extend to the outer wall of the artery, with a hypoechoic 'black' region around the blue of the lumen).*

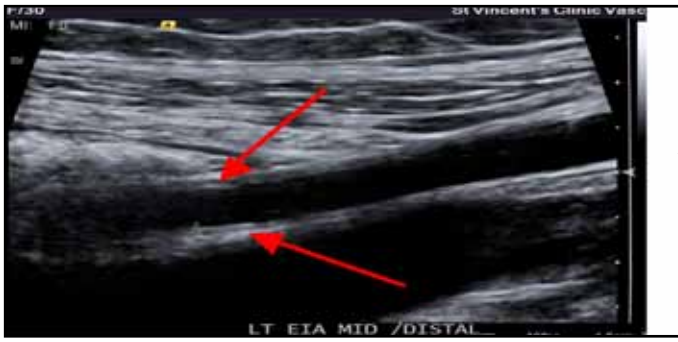


Figure 8: *Endofibrosis: B-mode sagittal view demonstrating EIA wall thickening (grey lines).*

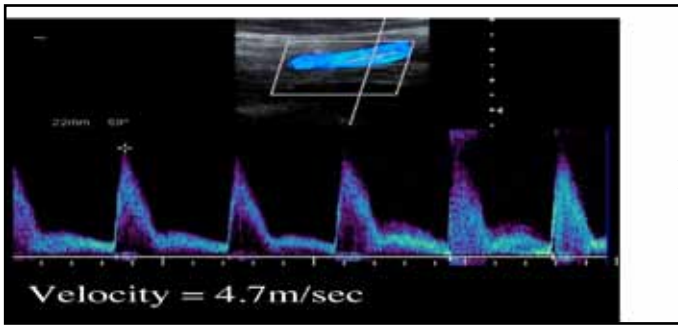


Figure 9: *Endofibrosis: Abnormally increased velocities (4.7m/sec) confirming a stenosed EIA.*

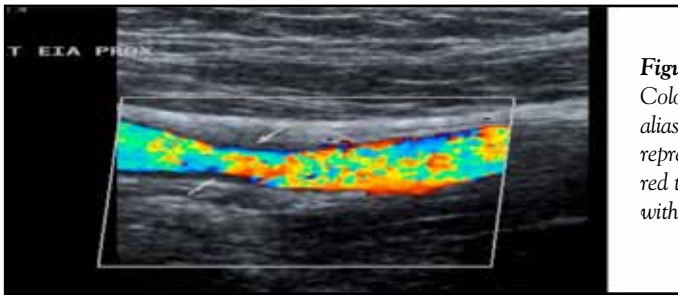


Figure 10: *Endofibrosis: Colour filling defect and aliasing (abnormal colour representation of blue and red together) associated with a stenosed EIA.*

A/Prof Debbie Marriott

Therapeutic drug monitoring of the β-lactam antimicrobial agents on the St. Vincent's Campus: a first for New South Wales

Infection and its consequences, whether community or hospital-acquired, are an important cause of morbidity and mortality in patients in the Intensive Care Unit (ICU) with death rates approaching 50%. Antibiotics have revolutionised medical care since their inception over 60 years ago. However, despite the availability of antibiotics that are active against almost all the bacteria causing serious infection, treatment failures still occur. One increasingly recognised cause of failure is the highly altered physiology of the ICU patient. Factors such as increased or reduced drug clearance by the kidneys, altered blood flow in the circulation (particularly in patients with septic shock), liver and heart dysfunction, and the amount of the antibiotic that is bound to proteins in the blood, all have a significant impact on the level of antibiotic in the blood, and therefore on patient outcome.

The β-lactam group of antibiotics, which are all related to penicillin, are commonly used as first-line therapy in the Intensive Care setting because they have a broad spectrum of activity against bacteria and very low toxicity. There is however considerable evidence that for the β-lactam drugs to be maximally effective in killing bacteria, prolonged high levels in the blood are critically important. As already noted, drug clearance from the body is significantly altered in septic ICU patients. However the dosage and timing of antibiotic administration is usually based on information obtained from healthy volunteers, and may be misleading and dangerous as the dynamic changes occurring in the septic patient are not taken into account.

A further issue in the ICU setting is patients supported on total heart-lung bypass or 'Extra-corporeal Membrane Oxygenation' (ECMO). This is undertaken in critically ill patients to

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

take over the role of their heart and/or lungs and involves pumping the patient's blood through tubing and oxygenation membranes outside the body. This has a significant impact on the effectiveness of many drugs administered as they can bind to the tubing or membranes, resulting in less drug reaching the sites where it is needed in the patient. There is very little published information on the effect of ECMO on antibiotic levels in the blood, particularly the β-lactam antibiotics which are often used in this setting. St. Vincent's Hospital provides a retrieval service for patients requiring ECMO and manages more patients on ECMO than any other hospital in New South Wales so acquisition of this knowledge is essential and would be of significant benefit to the patient.

It is possible to measure the blood levels of many drugs in common use in the ICU. This process, known as therapeutic drug monitoring (TDM) is vital in maximising drug effectiveness whilst minimizing toxicity in this challenging clinical setting. To date, TDM has only been performed routinely for one class of antibiotics – the aminoglycosides, which can cause significant damage to kidneys and hearing if the levels are too high. Despite the increasing evidence that low levels of the β-lactam antibiotics are common in septic patients because of their altered physiology, and that this has a significant deleterious impact on patient outcome, TDM was not routinely available for this class of drug and no clinical pharmacology units in New South Wales offered this service, despite the increased recognition of need.

Following a grant from a generous benefactor, therapeutic drug monitoring of a number of antimicrobial agents has been established in the Clinical Pharmacology Unit. Assays have been developed for the following βlactam drugs:-

- flucloxacillin, a critically important drug in the treatment of serious staphylococcal infection
- meropenem, a drug which is administered for resistant bacterial infections and meningitis
- piperacillin/tazobactam, a commonly used β-lactam with a broad spectrum of antimicrobial activity

A recent patient treated in the Intensive Care Unit at St. Vincent's hospital highlights some of the issues of treating serious infections in a septic patient and the importance of TDM to the solution.

A complex patient with a left ventricular assist device developed Staphylococcal aureus blood stream infection. He was treated with the recommended dose of flucloxacillin, 8 gm daily. His renal function was impaired so the consultant considered reducing the dose. However his blood cultures remained positive for 4 days despite seemingly adequate antimicrobial therapy given at the recommended dose. A flucloxacillin level was performed and was found to be very low. The dose was increased to 12 gm/day and the infection was cleared.

The ability to measure β-lactam antibiotic levels on campus with a rapid turn-around time will enable the dose, timing and mode of delivery of the drug to be optimized for improved patient outcome and will have a significant impact on our ability to treat complex septic patients.

Dr Jeanette Stewart

An Introduction to Neuropsychological Assessment

Dr Jeanette Stewart BSc(Hons), DPsych, Dip Clin Neuropsych
Clinical Neuropsychologist / Clinical Psychologist
Clinical Neuropsychology Services (CNS)
St Vincent's Clinic

Overview Including Historical Context

Neuropsychology is defined as the study of the relationship between behaviour, emotion and cognition on the one hand and brain function on the other.

The interest in the workings of the brain can be traced back to the ancient Egyptians who, although having a strong aversion to dissection of the brain, believed different parts of the brain were responsible for different functions.

Pythagoras, believed that thought processes and the soul of an individual were located in the brain and not the heart.

Hippocrates also believed that the brain was the seat of intelligence and was the first to recognise that paralysis occurred on the side of the body *opposite* the side of a head injury.

Galen (circa 200 BC), Andreas Vesalius (1514-1564), Rene Descartes (1596-1650) and Franz Joseph Gall (1758-1828) further refined knowledge of brain functioning and no introduction to this topic is complete without recognising the work of Paul Broca (1824-1880), who described expressive language deficits following strokes originating in the left hemisphere.

Somewhat later, Carl Wernicke (1848-1905) provided further insights into the nature of language comprehension when he described a number of patients with lesions of the superior posterior part of the left hemisphere. In contrast to the

expressive language deficits reported by Broca, Wernicke's patients presented with significant difficulties understanding language (receptive deficits).

To date there have of course been significant refinements in understanding the neuroanatomy of language functioning but the contributions of Broca and Wernicke were extremely important.

The need for the assessments of brain functioning evolved principally from the study of First World War veterans, as a means to understanding brain damage and to plan appropriate treatment. The war years, however, including those of the Second World War, really saw the refinement of techniques and development of the profession as it is today. Drawing heavily on the neurosciences and the philosophies that increasingly became aware of the link between mind and body, the study of psychology further developed the assessment methodology used today. The work of influential educational psychologists such as Jean Piaget (1896-1980) and Alfred Binet (1857-1911) prompted the development of a multitude of intelligence test batteries, further used for assessment and screening for educational purposes. These techniques were further refined with developments in statistical analysis providing the foundation of modern neuropsychology tools. There followed an explosion of research focusing on both 'normal' and 'injured' brains to provide the cognitive foundations of neuropsychology.

The contributions of Alexander Luria (1902-1977), Michael S. Gazzaniga (1939 -), Endel Tulving (1927 -) and Fergus Crail (1935 -) provided valuable insights into the psychological or cognitive abilities of various brain regions. However, the vogue of localising lesions gradually gave way to more holistic models and the advent of models emphasising connectionism, functional organisation and mental activity.

Neuropsychology today

Neuropsychology today is a broad science and together with the advent of modern imaging techniques, the discipline continues to investigate, research and learn more about the functioning of the brain. Modern clinical neuropsychology uses quantitative measures of cognition that are applied to a range of population-based scores from which deviations can be assessed in terms of clinical relevance. Diagnostic assessments provide assistance in patients with neurological disease or injury; monitoring recovery of function; or the effects of pharmacological treatment and surgical interventions; or distinguishing organic from psychological or functional conditions. Extensive research has yielded important profiles specific to various conditions: cortical versus subcortical pathology; the differential diagnosis of various progressive neurological conditions such as dementia; and the impacts of infective or toxic processes, or the focal cognitive impacts of stroke.

Clinical neuropsychologists assess individuals with cognitive difficulties including problems with attention, concentration, language, memory, visual spatial functioning and the so-called executive abilities (difficulties with problem-solving, decision-making, self-regulation, planning, abstract reasoning or other aspects of behaviour). The assessment and identification of cognitive impairments cannot be determined without specialist neuropsychological tools and techniques. Briefer screens of cognitive abilities such as the Mini Mental Status Exam (MMSE) may highlight potential problems in cognition, but the tools of neuropsychology are far more refined and scientifically valid instruments for accurate measurement.

The results from assessments are incorporated towards facilitating clinical diagnosis, management, outcome and rehabilitation. The emphasis of assessment is not limited to diagnosis, but includes clinical support, education and advice about how individuals can manage identified difficulties.

The diagnostic expertise of clinical neuropsychology is also combined with clinically relevant applications. Neuropsychologists are employed in acute health care, rehabilitation, aged care, paediatrics, educational facilities, in forensic environments and medicolegal consultation. Assessment findings can guide and facilitate return to work and provide information about civil capacities (for example, testamentary capacity or consent to treatment). Those employed in neurological rehabilitation also assess and provide treatment of underlying problems employing cognitive, educational, behavioural or psychosocial methods.

Neuropsychological Assessment

A neuropsychological assessment aims to assess an individual's cognitive strengths and weaknesses by relying on a range of specialised assessment tools. The assessment is composed of an in-depth clinical interview during which background information about patient's symptoms are obtained. Behavioural observations during the interview provide valuable insights into the individual's attention, concentration, language and information processing abilities. Symptoms not reported by the individual therefore may become readily apparent to the trained observer. The clinical interview consequently provides the foundation that determines the focus of assessment. Pertinent areas of enquiry include developmental and educational history, including medical, neurological and psychological history.

Neuropsychological tests are intrinsically performance-based. Individuals perform a variety of tests in the presence of the neuropsychologist. Self-reports of daily functioning as well as observations of behaviour while completing tests are also important sources of information.

Data Analysis

Scores from a neuropsychological assessment are converted to age scaled scores. These have a mean of 10 and a standard deviation of 3. A subtest score of 10 would indicate that the individual is performing within the average range relative to other individual's of his age.

However, to enhance reliability a number of different tests are administered for each cognitive domain. The auditory memory index on the WMS-IV for example, is composed of several subtests assessing auditory memory. These scores are aggregated into index scores that have a mean of 100 and a standard deviation of 15. So, an individual who has an auditory index score of 100 is performing within the average range when compared to the age related norms. Index scores are far more reliable and psychometrically robust than the individual subtest scores.

Scores from neuropsychological assessment must be interpreted in the

context of the individual's expected performance. For example, an individual's memory performance on assessment may fall within the average range when compared with age-matched norms. However, an average range memory performance may nonetheless provide evidence of an impairment when compared with the individuals overall intelligence or general ability.

An individual's pre-morbid functioning provides the basis from which current functioning can be compared and evaluated. The educational and occupational history is determined as this information provides information from which a change in functioning can be ascertained. High functioning individuals often pass bedside cognitive screening tasks such as the MMSE, as memory is correlated with intelligence. Cognitive screening tests of course have a well-established role in assessing cognitive functioning at the bedside or clinic. However, when results are interpreted without reference to the influence of an individual's pre-morbid intelligence, there is the possibility of misclassification. Hence, pre-morbid intelligence should always be considered when using screening tests.

There are specially devised neuropsychological tests that rely on abilities thought to be unaffected by cognitive decline associated with neurological damage. Reading is a skill less likely to decline in organic conditions and is highly correlated with IQ. There are specific tests of reading that can predict performance on a number of neuropsychological measures. The patient is asked to read and pronounce an irregularly spelled word. Reading such words means the individual will not be able to use the usual grapheme phoneme route to decode the word. For example, the 'gh' in *tough* is difficult to read unless an individual has prior knowledge of the word. Similarly, the word *heir* is often pronounced *hair* or the word *psalm* pronounced palm.

Reading accuracy scores allow for demographic prediction tables to be developed. These are further co-normed with standard neuropsychological tests. This allows for a comparative analysis between predicted and actual general intellectual and memory function.

By way of example, Table 1 shows an individual's performance on the auditory memory index. In this case, performance fell within the low average range (21st percentile) when compared with same aged individuals (the sample population or normative comparisons).

However, when the auditory memory index is compared with individuals matched for age and level of education (here the index is expressed as a T score), the performance is classified as mild to moderate impairment (5.5th percentile).

Therefore, reliance on an individual's performance compared with similar aged individual's may not reveal the extent of an impairment unless factors such as

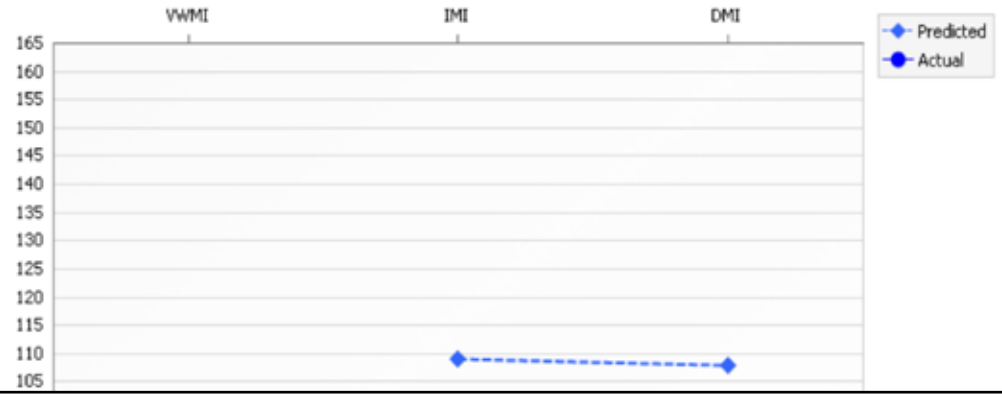
Table 1:

WMS–IV Full Demographic Adjusted Index Score Summary

	Age Adjusted		Full Demographic Adjusted		
Index	Index Score	Percentile Rank	*T* Score	Percentile Rank	Qualitative Description
Auditory Memory	88	21	34	5.5	Mild to Moderate Impairment
Visual Memory	73	4	25	0.6	Moderate Impairment
Immediate Memory	75	5	24	0.5	Moderate to Severe Impairment
Delayed Memory	81	10	30	2.3	Mild to Moderate Impairment

Table 1 showing performance on tests of memory functioning Figure 1 showing the comparison between predicted and actual performance on tests of immediate memory (IMI) and delayed memory (DMI)

Figure 1: WMS–IV Actual – Predicted Score Profile



education and occupation are taken into account.

The use of measures assessing pre-morbid ability (as discussed above) allows for actual memory performance to be compared with what is predicted. An individual with high levels of education, occupation and higher than average IQ would be expected to generate high scores on tests of pre-morbid ability. In Table 1, performance on memory testing fell significantly below expectations.

Statistically meaningful differences between two or more test scores must also be considered with respect to base rates, that is, how often a given discrepancy occurs within the normative population (i.e., healthy samples). Deviations from the expected performance may reach statistical significance, but the difference is not always clinically meaningful unless the discrepancy is also uncommon (rare) in the sample population. In Table 1, the magnitude of the difference was both statistically and clinically significant.

The tests themselves are a product of very sophisticated science and statistical methodology. Current tests are highly accurate and standardised with high predictive accuracy, reliability and validity.

The Neuropsychological Profile

The neuropsychological profile is composed of the pattern of individual test scores relative to expectations and in relation to neurological/radiological findings and reported changes in cognitive functioning. Individual scores are evaluated to determine a pattern of cognitive strengths and weaknesses and, in turn, to relate these scores with behavioural observations and the referral question. There are particular patterns of performance (or signatures), which have traditionally been associated with known patterns of pathology and neurological diagnosis. However, it is important to note that individual neuropsychological test results are themselves not diagnostically specific. Consequently, neuropsychological assessment results are not interpreted in isolation.

The Neuropsychological Report

In the author's opinion, in a clinical setting the neuropsychological report serves two masters; the referral agent and equally important, the patient. Addressing the referral question of course shapes the report but results should and must be communicated to the patient and family where applicable. A caveat of course is when requests for neuropsychological assessments are received within a medicolegal context. In these cases lawyers may or may not make available to their client the results from an assessment and usually no further communication between the client and neuropsychologist takes place.

In clinical practice, a review appointment is usually, if not always, offered to the patient. This is the author's preference. Where this is not possible a telephone discussion can be organised. In some circumstances neuropsychological reports are also sent to the patient or a summary report can be tailored and forwarded. The author believes in a strengths based approach to feedback tempered with honest and supportive discussion of weaknesses. The purpose of feedback is not to provide rehabilitation. However, strategies should be given where weaknesses are identified and these can easily be incorporated into the report. The author also recommends reading lists to the patient (or carers) and provides advice regarding potentially useful professional organisations that may be relevant to further address identified weaknesses. Onward referrals are made to relevant agencies including clinical psychologists or neuropsychologists specializing in rehabilitation. The author also invites patients to initiate further contact if this might be helpful.

Conditions Assessed by Neuropsychologists

As alluded to above, neuropsychologists have been involved in the assessment of cognitive impairments in a wide range of conditions including cerebrovascular disease, epilepsy, neurosurgical conditions, trauma, tumor, infections, general medical conditions, drug and alcohol problems, psychiatric conditions and progressive neurological conditions such as dementia, Parkinson's disease or mild cognitive impairment (MCI).

Neuropsychologists specialise in adults, children and early development and there are services in private, public, forensic, medicolegal and educational facilities.

When referring a patient for neuropsychological services it is important to ensure the psychologist has specialist qualifications and is endorsed in clinical neuropsychology. Endorsement of a psychologist's registration is a legal mechanism under National Law that requires the Psychology Board of Australia to identify practitioners who have specialist clinical qualifications and advanced clinically supervised practice.

A Few Clinical Examples

Alzheimer's Disease

Alzheimer's Australia (2011) figures suggest that approximately 269,000 Australians were diagnosed as having dementia in 2011, with figures expected to rise to approximately one million by 2050. Accurate diagnosis of memory impairment is important in the context of excluding reversible causes of dementia in addition to guiding treatment and monitoring outcome. In addition, neuropsychological assessment has been shown to significantly increase diagnostic accuracy in dementia even after specialist medical evaluation.

The National Institute on Aging and the Alzheimer's Association work group diagnostic guidelines for Alzheimer's disease were updated in 2011. The criteria have followed research findings highlighting the clinical profile at the early stages of the disease prior to the development of the full clinical syndrome.

Neuropsychological research has played a central role in characterising the clinical profile of dementia associated with Alzheimer's disease (AD). The identification of early cognitive markers of Alzheimer's disease has allowed for early disease detection to facilitate intervention such as those offered by pharmacological agents (e.g., Aricept) and also to assist with differential

diagnosis. The cognitive 'footprint' of AD differs from that observed with normal aging and other conditions that may lead to dementia (for example, vascular disease, Lewy body disease or stroke related cognitive problems). The revised criteria for AD dementia include the identification of two or more impaired areas of cognitive functioning (or domains), falling below expectations, but in addition, are associated with a decline in functional status.

The clinical diagnosis of AD is facilitated, therefore, by assessing areas of cognitive functioning and identifying patterns of weakness and strength. Healthy aging is associated with mild word-finding difficulties, particularly for names, and slower information processing. While this can be worrisome, it is not clinically relevant. In contrast, cognitive difficulties that characterise early presentations of AD primarily reflect the involvement of areas within the medial temporal lobe, particularly the hippocampus. These areas of the brain are recognised as being critically important for the formation of memory. At the early stage of AD, neuropsychological assessment reveals a classic pattern of impaired learning, retention and recall in the context of otherwise intact cognitive functioning. Findings on assessment are demonstrated on measures of auditory and visual memory (e.g., prose recall, paired associate learning, design copy and recall tasks) with evidence of poor encoding, consolidation and recall. In contrast to the cognitive profile in normal aging, individuals with AD are impaired at recognition memory tasks. The memory profile in AD reflects rapid forgetting of new information, while autobiographical memory remains intact, at least in the earlier stages.

Impaired object naming and verbal fluency are also observed, particularly as the disease progresses and impinges on areas necessary for storage and content of semantic memory. With the passage of time, the disease progresses to other cortical regions gradually impacting on more global cognitive functioning and this is accompanied by increasing functional deterioration.

Neuropsychological assessment is therefore clinically relevant in identifying known cognitive markers associated with the disease progression, in addition to monitoring treatment response.

Mild Cognitive Impairment (MCI)

The term Mild Cognitive Impairment has been used interchangeably with preclinical AD, incipient dementia and isolated memory impairment, to describe those individuals who do not meet criteria for dementia, but on neuropsychological assessment have identifiable memory impairment beyond that predicted by age or level of education and in whom no other identifiable medical, neurological or psychiatric diagnoses has been identified. The isolated memory deficit does not impact functionally or does so minimally.

The diagnosis of MCI had initially been intended to facilitate the identification of cognitive impairment at an early stage and due to observations that some of these individuals convert later to AD. Earlier diagnostic criteria for MCI were limited to the identification of individuals in whom cognitive impairment was observed in memory (a single domain). However, more recently, there has been a recognition of non-amnestic forms, which involve other cognitive domains (so called, multi-domain), such as those presenting with primiarly impaired executive deficits. Such cases are termed non-amnestic MCI.

Unlike the diagnosis of AD, in which functional impairment is necessary, amnestic or non-amnestic MCI requires intact, or so called 'normal', functional ability.

The most recent recent diagnostic criteria for MCI states there must be:

(1) a change in cognition recognised by the affected individual or observers;
(2) an objective impairment in 1 or more cognitive domain/s;
(3) independence in functional activities; and
(4) the absence of dementia.

Under the new criteria, minor alterations in the degree of functional independence are permissible. However, this has been criticised as blurring the distinction between AD and MCI such that those currently diagnosed with milder stages of AD dementia, might under the new criteria be reclassified as having MCI.

Neuropsychological assessment facilitates the diagnosis of MCI diagnosis in addition to monitoring the evolution of cognitive and functional symptoms. The assessment includes an examination of various cognitive domains, analysis of informant-based measures of behavioural/functional abilities and assessment of competency in various instrumental activities. In particular, it is crucial to identify subtle deficits that may otherwise elude detection, particularly in those individuals of superior baseline intellectual ability.

Neuropsychological assessment therefore facilitates the differentiation of normal aging, dementia and depression, and in epidemiologic studies has been found to accurately predict conversion to Alzheimer's disease. Mild cognitive impairments can be identified that are otherwise not immediately obvious on clinical interview and are not necessarily identified with neuroimaging. The identification of impairments facilitates the discrimination of various MCI subtypes, monitors response to early pharmacological intervention and is helpful in determining conversion rates to varying types of dementia.

Neuropsychological Profile in fronto-temporal dementia (FTD) subtypes

In fronto-temporal dementia, there is relatively preserved memory functioning that contrasts with that found in Alzheimer's dementia. Instead, the predominant clinical features reflect alterations in personality, social skills, motivation, reasoning and language functioning. Because of their behavioural nature, symptoms can be mistaken for psychiatric conditions. Age of onset in FTD is much younger than AD. Clinical symptoms for a subset of FTD patients might also include extrapyramidal or motor neuron involvement as the disease progresses.

The neuropsychological profile in FTD reflects the underlying and varying pathology relating to the progressive degeneration of the temporal and frontal lobes of the brain. The symptoms in FTD however, are related to the areas of brain involved, not the pathology itself.

With refinements in research and imaging methodology, specific syndromes

are described within the broad term FTD. These reflect distinct clinicopathological findings on radiological imaging (MRI/CT) and confirmed by studies using meta analysis.

These subtypes include: behavioural variant FTD, (also historically called frontal variant FTD or Pick's Disease); semantic dementia; and progressive non-fluent aphasia (PNFA).

The term behavioural-variant FTD describes the syndrome reflecting pathology that initially affects the frontal lobes leading to the changes in personality and behaviour including loss of insight, stereotyped perseverative behaviour and often, quite profound changes in social behaviour and conduct. The behavioural variant, particularly in the early stages, is often characterised by a normal neuropsychological profile but in the context of significant behavioural and functional deficits. It reflects pathology affecting mainly fronto-median structures.

Patients with semantic dementia present with fluent aphasia accompanied by a progressive loss of knowledge of word meaning. In contrast, patients presenting with PNFA have expressive non-fluent speech patterns and have impairments with the phonology and syntax. These language-based syndromes are clinically and anatomically dissociable but broadly reflect pathology stemming from regions in the left temporal lobe.

In-depth neuropsychological assessment of behaviour, executive and language function significantly assists with the diagnostic process in discriminating these subtypes, in addition to distinguishing them from other neurodegenerative disorders. Research has identified reliable cognitive profiles relating to these three FTD syndromes but there is nonetheless some significant overlap between language and behavioural variants.

Neuropsychological tests of language functioning can help to identify and differentiate the various language variants. Language disorder variants associated with temporal lobe pathology lead to a breakdown in semantic system (or meaning system) of language. The cognitive profile of semantic dementia reflects a loss of meaning for words with gradual loss of comprehension, which also impacts negatively on reading and spelling. On testing, these patients have difficulty providing definitions of objects or words. Naming to confrontation may be intact but in the absence of comprehension for the named item. General and day-to-day memory often remains intact.

In contrast, the clinical feature of PNFA presents clinically with striking difficulties with verbal expression. Memory, comprehension and other neuropsychological domains remain intact, but language is characterised with distortion of speech, often being slow and hesitant, with a tendency to produce the wrong word or make grammatical errors. Comprehension for spoken and generated words is preserved, however writing and spelling is frequently impaired from an early stage, and can be accompanied by subtle changes in executive functioning. Behaviour is generally unchanged in the early stages though, because insight is preserved, there are high rates of distress in PNFA patients secondary to expressive language difficulties.

Case Example: language variant Logopenic Progressive Aphasia.

Logopenic Progressive Aphasia (LPA), a language variant of FTD, is characterised by slow speech and impaired syntactic comprehension and naming.

Table 2 below shows the results from neuropsychological assessment of a 62-year-old female who presented with progressively deteriorating cognitive symptoms, comprising difficulties with naming, pronunciation of words and a greater difficulty retrieving unusual or low frequency words (compared to common and high frequency words). Bedside testing of the patient had revealed particularly low scores on language and verbal fluency tests but with preservation of other abilities (namely, orientation and memory). The request for neuropsychological assessment followed subjective complaints relating to significant problems with word finding difficulty, remembering names and difficulty with naming objects, with a tendency for the patient to use alternative descriptions.

The patient's cerebral MRI was reported as showing marked asymmetrical cortical and subcortical atrophy involving the left temporal pole. Atrophy was limited to the anterior left temporal lobe, with the frontal lobes and the remainder of the brain appearing normal in volume and with both hiccocampi being normal in size and signal.

On clinical and neuropsychological assessment (using the Wechsler Adult Intelligence Scale, fourth edition (WAIS-IV), expressive speech was characterised by difficulties with word retrieval, in addition to an over reliance on gestures and hand signals to emphasise points or

Table 2: WAIS–IV Full Demographic Adjusted Composite Score Summary

	Age Adjusted		Full Demographic Adjusted		
Composite	Composite Score	Percentile Rank	*T* Score	Percentile Rank	Qualitative Description
Verbal Comprehension	76	5	30	2	Mild to Moderate Impairment
Perceptual Reasoning	96	39	46	35	Average
Working Memory	89	23	40	16	Low Average
Processing Speed	120	91	62	89	Above Average

descriptions. Receptive language was intact on casual conversation and on more basic tests of language functioning.

The neuropsychological profile was characterised by significant impairments in expressive language functioning. Naming to confrontation was significantly impaired but comprehension for unnamed items was strikingly intact (demonstrated by gesture or alternative description). Executive functioning was also significantly impaired by language-based tests. Non-verbal based tests (Perceptual Reasoning), in contrast, were performed within the average range. There were lateralised memory impairments with disproportionate auditory verbal deficits relative to visual memory abilities, and were considered secondary to expressive difficulties. Speeded information processing (Processing Speed) was remarkably intact.

The exclusion of other neurodegenerative conditions or reversible causes for the presentation lead to a diagnosis of probable logopenic aphasia. Follow up review was recommended in order to monitor the clinical progression.

Funding

At present there is only limited public access to neuropsychological services under the Department of Veterans Affairs (DVA), Workcover, the Motor Accidents Authority, Transport Accident Victims Compensation (TAC), and some health care funds and public hospitals. Neuropsychological services are not currently rebated under Medicare and, as such, many Australians are not in a position to access services.

Conclusions

Neuropsychological impairments contribute significantly to disability, but unlike physical disability, are often not immediately obvious. Nonetheless, these disabilities can be acute, chronic or progressive and have serious implications for an individual's independence, employment, community engagement and family life. Indeed, figures from the World Health Organisation highlight that brain diseases and disorders account for the largest proportion of medical disability in the developed world, Neuropsychological assessment has been termed, "*a valuable clinical tool that provides unique information about diagnosis, prognosis, and clinical management for nearly all neurocognitive and psychiatric disorders as well as many medical conditions*".

It is imperative that the Government seek to fund neuropsychological services to facilitate accurate and early diagnosis so patients may receive appropriate intervention and treatment. The present system inevitably creates inequity in provision and access to services.

Useful References

1: **Neuropsychological Assessment: A Valuable Tool in the Diagnosis and Management of Neurological, Neurodevelopmental, Medical, and Psychiatric Disorders.** Braun, M et al (2011), *Cognitive & Behavioral Neurology. 24(3)*:107-114, September 2011.

This article provides a useful summary of the contributions from neuropsychological assessment in clinical practice across a number of diagnostic categories.

2: **Neuropsychological Evaluation in Primary Care..Michels TC, et al** *American Family Physician*. 2010 Sep 1;82(5):495-502.

This article is directed toward adult patients in whom a more formal assessment of the interaction among neurologic, psychological, and behavioral function is warranted

3: Dementia Spending: Missing early diagnosis and treatment planning.

http://www.hospitalandagedcare.com.au/news/dementia-spending-missing-early-diagnosis-and-treatment-planning[1]

The national Chair of the Australian Psychological Society College of Clinical Neuropsychologists, Dr Fiona Bardenhangen, points out that government funding providers are aware of the important role that neuropsychologists can play in early diagnosis and treatment planning. Despite this there is limited government support of neuropsychological services, with only the Department of Veteran's Affairs and some third-party insurers, such as Workcover, covering neuropsychological assessments.

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Asso Prof Ian Woodgate
Dr Oliver Khoo

Sacroiliac Joint Arthrodesis via the Ilio-Inguinal Approach: A Case Series of 53 Fusions

Associate Professor Ian Woodgate

Dr Oliver Khoo

Summary

Sacroiliac joint arthrodesis (SJA) is the treatment of choice for sacroiliac joint (SIJ) pain which cannot be managed by non-operative treatment. Open and percutaneous surgical techniques have been used for SJA but currently no technique is universally recognised as being superior. Evidence in the literature is inconclusive with published reports on techniques for SJA involving only small numbers of patients. We present the results of our experience of 53 fusions performed via the third window of the ilio-inguinal approach, the largest series in the literature to date.

Introduction

It has been known for many decades that sacroiliac joint disorders can generate low back pain and surgical solutions have been sought since at least 1926.[1] Recent reports estimate the incidence of sacroiliac joint pathology in patients with low back pain to be approximately 15%[2] but perhaps as high as 30%[3]. This high percentage contributes to the large economic cost of back pain which is estimated at $175 million directly from medical care in 2001 and estimated to be as high as $8.1 billion from lost work time, with the rate of contributing factors such as physician visits and work hours lost having changed little since 2001. These figures are similar internationally.

Causes of sacroiliac joint pain vary widely with a recent study indicating the cause to be trauma in 44% of patients, idiopathic in 35%, and in 21% pain was secondary to the cumulative effects of repeated stress leading to both inflammatory and non-inflammatory pathology. It is also worth noting the possible effect of femoroacetabular impingement on motion of the sacroiliac joint, whereby impingement due to the movement of the femur against the pelvis translates into stress at the sacroiliac joint with subsequent pain.

Sacroiliac joint pain is often misdiagnosed, resulting in multiple investigations and a delay in diagnosis. At present, the best diagnostic investigation

Associate Professor Ian Woodgate MBBS (Hons), FRACS (Orth), FAOrthA
Dr Oliver Khoo MBBS, FRACS (Orth)
Research Fellow, Orthopaedic Department
St Vincent's Hospital

is the sacroiliac block performed under image guidance[2,3,6,7,10]. The use of a "Flamingo" or "Stork", one leg at a time standing pelvic film is also useful in identifying instability[5] at the sacroiliac joint (see Figure 1), where there is generally considered to be very limited motion in any plane[5,8,9]. Physical examination techniques are poor discriminators when used in isolation [2,3] and standard radiographic investigations are similarly deficient. Computerised Tomography (CT) of the sacroiliac joint has been shown to be of limited diagnostic value[4], while Magnetic Resonance Imaging (MRI) may be useful for identifying soft tissue tumours and early inflammatory changes associated with spondyloarthropathy[5]. Bone scanning may be most useful in identifying early stress fractures, inflammatory and infectious conditions [5].

Non-operative treatment may be useful as both a bridging and a definitive treatment and can include physiotherapy and chiropractic manual therapies, exercise programmes, intra-articular injections, prolotherapy and radiofrequency neurotomy. Treatment is directed partly by the cause. For example, sacroiliac joint pain associated with pregnancy typically resolves with parturition while inflammatory arthropathies typically go on to resolution by ankylosis. Surgical intervention is usually reserved for cases which have failed non-operative management.

Since Smith-Petersen and Rogers first advocated for sacroiliac joint arthrodesis in treatment of arthritis of the SIJ,[1] there have been several different techniques published, typically involving case series, of which the largest appears to be only 20 patients. Here we report the results of a retrospective review of sacroiliac joint arthrodesis performed through the third window of the ilio-inguinal approach.

Methods

We performed a retrospective review of the case files and radiographs of all patients who had been treated with a sacroiliac fusion after failing non operative management over the last 10 years. Each patient's file was reviewed for details of their demographics, the history of the presenting illness, examination findings, investigations, non-operative treatment and operative results.

Findings

From 2001- 2011, 53 sacroiliac joint fusions in 43 patients (30 female, 13 male) were performed. Patients had a mean age at presentation of 55.4 years (range from 21 to 86 years) with an average weight of 73kg, average height of 168cm and an average Body Mass Index (BMI) of 25.8. The history of the presenting illness varied between patients but all patients did report pain. Patients localised their pain to the ipsilateral posterior pelvis in 85% of cases but a small number of patients also experienced groin and lateral sided pain. 20 patients reported pain which led to functional limitation with patients having difficulty completing their work and their activities of daily living. Difficulty whilst walking was a common complaint and 12 patients had noticed they walked with a limp. 13 patients complained of a painful clunk localised to the ipsilateral sacroiliac joint, which has been considered a pathognomonic sign for instability. More uncommon symptoms were posterior crepitus over the affected sacroiliac joint in 3 patients and stiffness in 2 patients. Patients' past histories included spine surgery in 11 patients, total hip arthroplasty in 5 patients and hip arthroscopy in 2 patients. With regards to

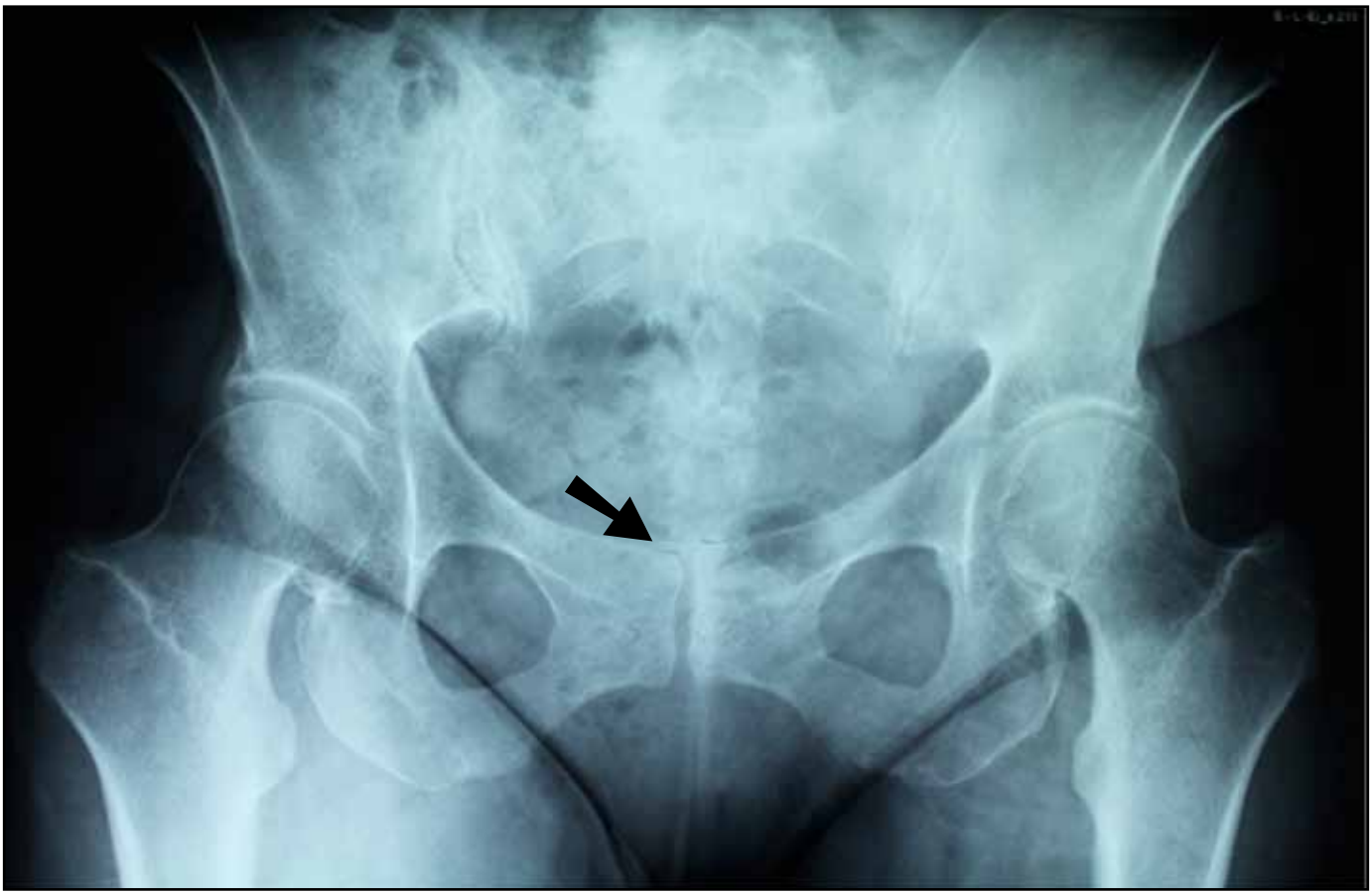

Figure 1 *Flamingo radiograph demonstrating pelvic instability at the pubic symphysis*

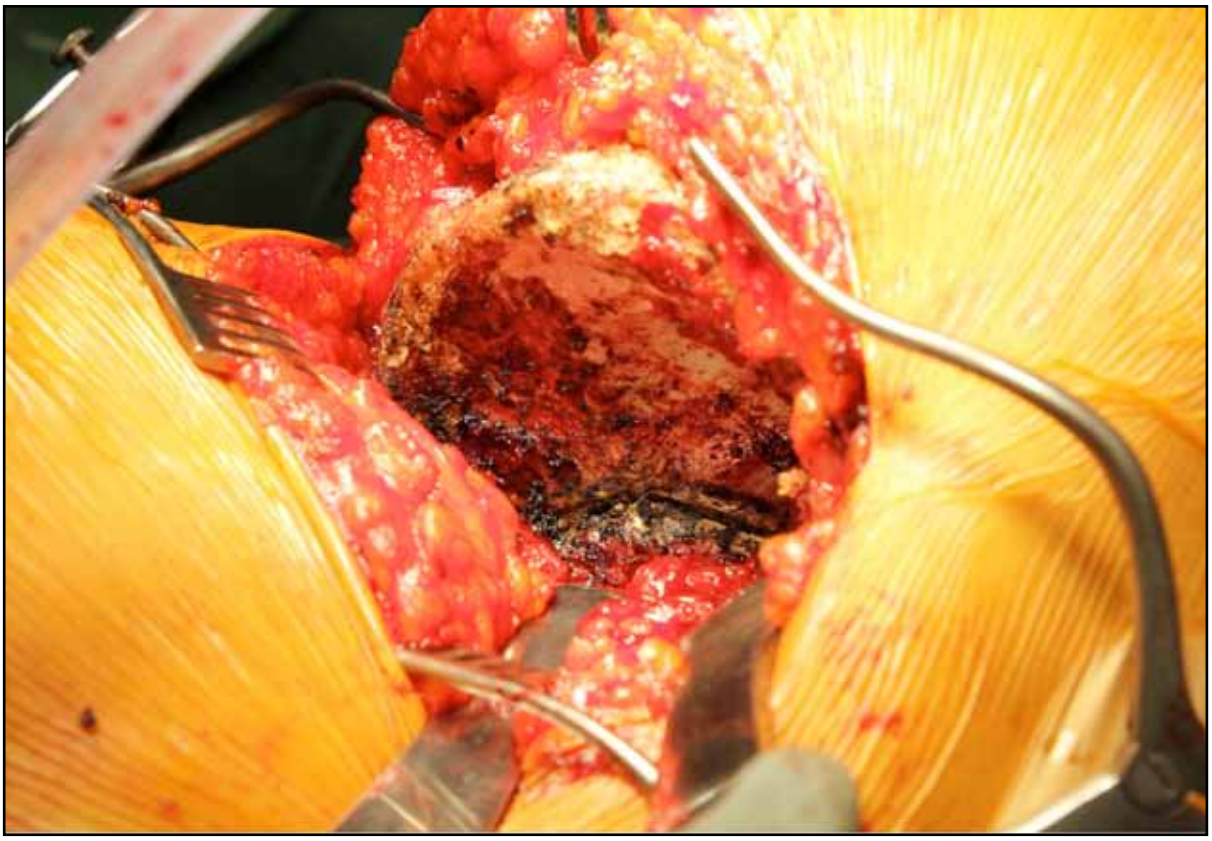

Figure 2
Intraoperative photograph of the sacroiliac joint exposure

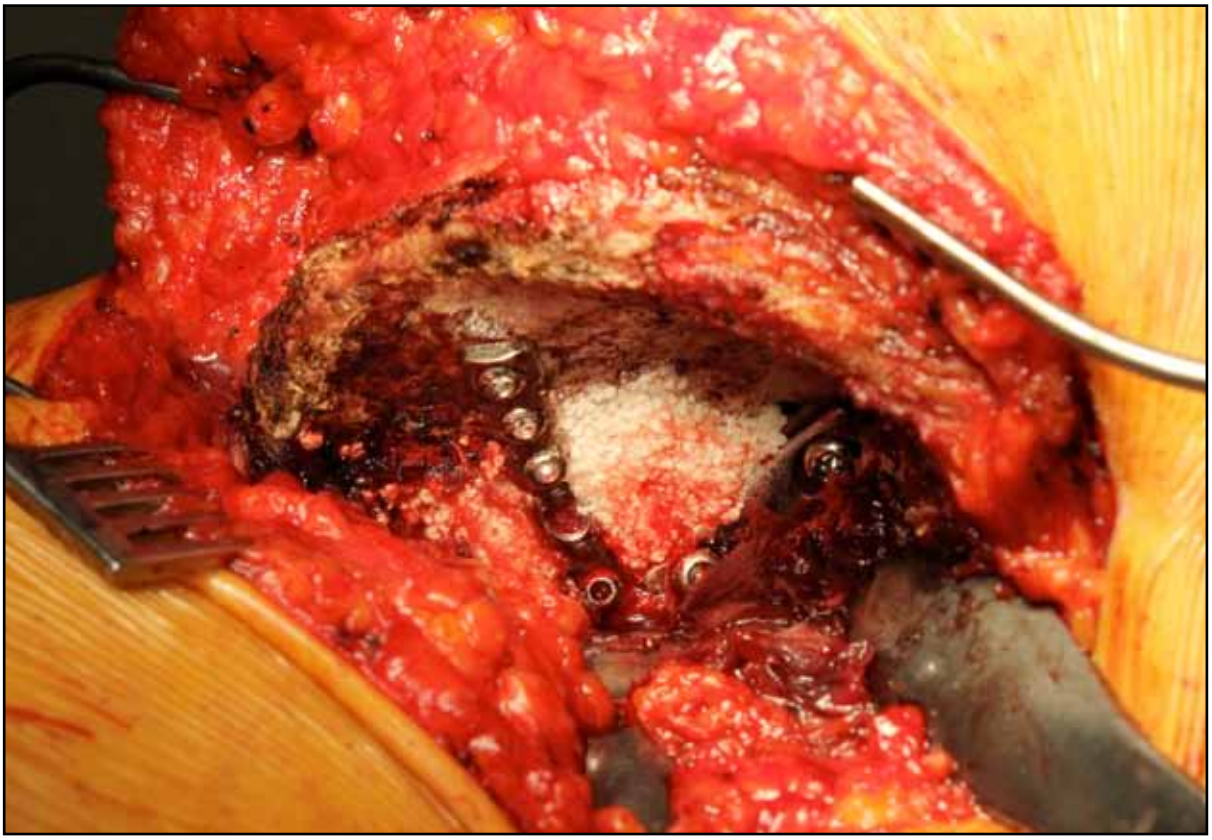

Figure 3
Intraoperative photograph with hardware and bone graft in place

risk factors for nonunion, 7 patients were cigarette smokers, 2 patients had diabetes mellitus and 2 patients were on corticosteroids. 5 patients were employed in manual labour and 13 cases were the subject of workers compensation claims. The most common cause of sacroiliac joint pain was trauma, with 36 patients reporting a traumatic event (14 of these cases were motor vehicle accidents including pedestrians). In 3 patients pain was attributed to post-partum instability.

On examination, most patients walked with an abnormal gait. 20 patients demonstrated a positive Trendelenburg sign and 3 had buttock wasting. Tenderness over the sacroiliac joint was common, being present in 30 patients. Range of motion was restricted in 2 patients. With regards to provocative tests, springing of the pelvis caused pain in 4 patients and the FABER (Flexion ABduction External Rotation) test was positive in 30 patients. One patient had crepitus at the SIJ on movement of the ipsilateral hip.

In total, 95% of patients required some form of analgesia to treat their pain. 29 patients required an opioid-based analgesia while 15 patients required anti-inflammatories. There was some overlap between these groups.

All patients had undergone multiple investigations prior to receiving specialist referral. Radiographs had been performed in all patients and commonly included pelvic, lumbar spine and hip radiographs. 25 patients had been investigated with CT scans and 12 had been investigated with MRI. Bone scans had been performed in 29 patients. To confirm a diagnosis of sacroiliac disease the most common test ordered after specialist review were Flamingo radiographs.

Nonoperative management was attempted in all cases, including simple analgesics, anti-inflammatories, physiotherapy, SIJ prolotherapy injections, hydrotherapy, massage, ultrasound, a belt, acupuncture and chiropractic manipulation. There was a trial of non-operative management for an average of 32 weeks prior to operative intervention.

Surgical Management

Operative management was the same for all patients and consisted of fusion of the sacroiliac joint via an open approach through the third window of the ilioinguinal approach (see Figure 2). The patient was positioned supine on the operating table. Anaesthesia consisted of general anaesthetic in 50 patients and spinal anaesthetic in 3 patients. All patients received a Trans-Abdominal Plexus (TAP) block. After the sacroiliac joint was exposed, debridement of the joint was performed by means of curettage and burr. Fixation was then inserted consisting of 2 plates and their associated screws (2-hole DCP with 6.5mm screws and 5-hole 3.5mm reconstruction plate with 4mm screws). Artificial bone graft substitute was implanted (see Figure 3). Routine antibiotic prophylaxis consisted of intravenous administration of a first generation cephalosporin. Thromboprophylaxis consisted of subcutaneous enoxaparin (40mg, once daily) and compression stockings. A drain was placed in situ for 48 hours. Follow up consisted of regular review at 2, 6 and 12 weeks, 6 months and 1 year. Radiographs were routinely performed immediately and at one year post operation. Radiographs were assessed for hardware position, pelvic movement (on Flamingo views), successful fusion and any complications.

Results

The mean follow up period was 148 weeks (range 44 to 480 weeks). All patients had an improvement in symptoms. 90% of patients reported a reduction in pain. All patients with bilateral disease improved with the surgery to fuse their first sacroiliac joint and returned for surgery to fuse the other side. Radiographic features of fusion could take up to a year to be seen. Of the 33 cases whose follow up was one year or greater, all radiographs demonstrated successful fusion of the sacroiliac joint. Of the remaining 20 cases whose follow up was less than one year, 3 had radiographs which demonstrated fusion and there were no signs of hardware complications with respect to implant position, implant breakage, loosening or lysis around the screws to indicate movement at the sacroiliac joint. There were 2 cases of transient lateral femoral cutaneous nerve parasthesiae. There was one case of a below knee Deep Vein Thrombosis (DVT) which was treated with enoxaparin and subsequently resolved.

Conclusion

Fusion of the sacroiliac joint is successfully performed via the Ilio-Inguinal Approach. Consideration for surgery can be given to patients who have failed non-operative management.

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  "Use of fibroblast derived stem cells to define the role of GATA1 and p53 in normal haematopoietic and leukaemic stem cells with trisomy 21"

- **Tancred Research Grant – $67,000**
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- **Multidisciplinary Patient Focused Research Grant 2 – $25,000**
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