PROCEEDINGS

ST VINCENT'S CLINIC, SYDNEY

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EDITORIAL

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Consultant Neurologist

Editor, Proceedings

This Issue of Proceedings comprises eight articles from several different fields of medicine. Unfortunately it was not possible to obtain a summarised transcript of the 2002 Sandra David Oration which was given by Dr A Kass, MD, of the Johns Hopkins Medical Institute, Baltimore. This oration was dedicated to the memory of the late Ray Kelly who was one of Dr Kass' Fellows during Ray's period of post-graduate study in the United States.

Obesity is a topical issue in our society. It is now epidemic in Australia with a prevalence of approximately 60%. It is timely, therefore, to have an article on that subject, by Dr Katherine Samaras, endocrinologist. Her article is complimented by a practical approach to weight loss as suggested by Dr David Mann, nutritionist. The articles should provoke thought, and action, amongst a good proportion of readers!

Coronary stents are common amongst our aging population and Dr Paul Roy, cardiologist, has reviewed this topic especially with respect to its development at St Vincent's. Dr Roy is a very busy clinician and the excellence of coronary stenting at St Vincent's can be largely attributed to his carefully compiled database, constant self-audit, retraining and revision of the technique.

Dr David Williams, gastro-enterologist, has reviewed the subject of endoscopic ultrasound, a specialised technique performed in Sydney only at St Vincent's (by David) and Concord Hospitals. This new technique has revolutionised the investigation of suspected pancreatic tumours and mediastinal masses as well as greatly assisted in the staging of gastrointestinal cancer. Dr Carolyn Bariol, gastroenterologist, has provided an overview of inflammatory bowel disease and specifically has reviewed an early trial at St Vincent's using thalidomide for those conditions. This is promising to be a very effective therapy.

Cochlear implants have had an enormous positive impact on the lives of patients with profound deafness. The first such implant in Australia was performed by Dr John Tonkin, ENT surgeon at St Vincent's. Our youngest cochlear implant specialist at St Vincent's, Dr Phillip Chang (ENT surgeon), has reviewed the current situation with respect to that specialised surgical procedure. St Vincent's continues to be a leader in the combined ENT and Neurosurgical approach to certain skull-base tumours. I have included in this Issue a case report by Dr Pedro Valente, visiting Fellow under Dr Paul Fagan, on the subject of a rare complication of acoustic neuroma surgery.

Spinal problems are common in our community and the physiotherapy department of St Vincent's Clinic provides wonderful support for the many spinal patients who come through our doors. Members of that department formed part of a collaborative trial run by Professor Jull, physiotherapist, analysing the benefits of physiotherapy for cervicogenic headache. The results of that study are reported.

St Vincent's Private Hospital and Clinic Ladies Committee have continued their wonderful fundraising for research on St Vincent's campus. Over the last financial year they made $160,000 available to fund three separate Sr Mary Bernice Research Grants. The successful grant applications for 2003 are listed at the end of this Issue. In addition to the above, this year the St Vincent's Clinic Foundation announced it would commit a minimum of $1,000,000 over the next three years to fund adult stem cell research on St Vincent's campus.

Dr Katherine Samaras

And the winner in the newest epidemic category is ... OBESITY

INTRODUCTION

In almost every facet of the modern medical practice, we are confronted by the compounding problem of obesity. Obesity predicts the development of Type 2 Diabetes, ischaemic heart disease and is closely associated with hypertension, lipid disorders, sleep apnoea, infertility and degenerative joint disease. Obesity exacerbates the disability of neurological, orthopaedic, respiratory and rheumatological conditions. Obesity is also associated with higher risks of common cancers, such as bowel, ovarian and breast cancer. Obesity significantly increases the morbidity associated with anaesthesia and surgical complications, both early and late.

Recent Australian data have shown prevalence rates for overweight and obesity to have reached epidemic proportions. Approximately 50 per cent of all women and 60 per cent of all men, aged 18 or over, are either overweight or obese. The statistics are even higher in certain ethnic groups. Rates of childhood obesity are also increasing rapidly. Australians are now the second most obese nation in the world, closely following the trends found in the United States. Since obesity (specifically central abdominal obesity) predicts important diseases such as diabetes, hypertension and cardiac disease, the current rise in obesity prevalence is likely to be followed by increased rates of these conditions and their sequelae.

One of the great difficulties in treating obesity is the apparent lack of any intervention that provides long term amelioration. Diet and exercise programmes have been proven to lack long term efficacy. Obesity is characterised by high rates of what has been termed by some as “recidivism”, implying that patients who actively lose weight through dietary restriction and increased energy expenditure, lapse back into “old habits” with consequent weight regain. The physiology of the adipocyte and whole body metabolism demonstrates that the problem is far more complex than adherence to dietary and physical activity guidelines. The notion that the higher fat mass that must be re-established (the “adipostat”) will be elaborated upon subsequently.

Dr Katherine Samaras MBBS, PhD, FRACP
Consultant Gastroenterologist
St Vincent’s Clinic

Understanding this physiology allows us to guide our patients through obesity to a healthier body mass, but is the most compelling argument for strategies for obesity prevention.

In patients who are overweight or obese, a reduction of 5kg alone, is often sufficient to ameliorate the metabolic consequences of obesity. Patients often hold the absurd notion that they have to reach a specific weight for their height, dictated by life insurance tables.

This may be an unreasonable ask for the patient and is usually not necessary for health benefits.

Appropriate short and long term goals will depend on the dietary strategy selected.

Defining overweight and obesity

Whilst the body mass index (BMI) is a useful indicator of obesity, it is a crude estimate of body fat mass, as it is confounded by lean tissue mass. The BMI is a far less accurate indicator of fat mass in muscular men, for example, or ethnic groups with a high lean tissue mass, such as South Pacific Islanders.

The BMI provides insufficient clinical information regarding an individual's risk from the sequelae of obesity. The waist circumference is a critically important measure in this regard, as it is a better clinical risk indicator and allows the identification of central obesity. The waist circumference is a simple measure and requires only a tape measure. Waist circumference is measured at the narrowest point between the ribs and the iliac crest. In some patients, especially the centrally obese, such a point won't be identifiable. The level of the umbilicus is a suitable alternative. Central obesity is present when the waist circumference exceeds 90 cm in a female and 100 cm in a male.

Understanding the aetiology of obesity

Population studies demonstrate that genetic factors explain up to 60 per cent of the differences between individuals in total body fat mass and its distribution.[1] Despite the strong genetic contribution to body fat mass, only a few genetic mutations have been described. These account for less than a dozen cases of obesity world wide, almost all manifesting as morbid obesity in early childhood. These include mutations in the leptin gene, the leptin receptor gene and other genes involved in the regulation of hunger and satiety.

Obesity is mostly due to a long term excess of energy intake over energy expenditure in individuals who have a genetic predisposition for excellent energy conservation. These "thrifty" genes were quite useful in circumstances of privation, such as famine or cycles of war, when food availability was low and this was an excellent survival advantage. The genes that regulate the effective storage of energy are unlikely to be mutations, but genetic polymorphisms that have arisen from long term adaptive changes or selection by attrition during adverse conditions such as cycles of famine or war. The current physical environment in Australia is, however, one of perpetual feast for most, married to increasing sedentariness. Such an environment will permit genetically predisposed individuals to accumulate a larger amount of body fat, compared to others who do not possess such "thrifty" genes, and this is a useful model for understanding the disparity in body fat stores between individuals in a society where most observe similar lifestyles.

Whilst this permits us to understand why certain individuals develop obesity, it does not help understand why many patients do not seem to be able to maintain any hard won loss of fat mass. Here, the notion of the "adipostat" is helpful. This refers to a physiological state of homeostasis that is established at the high body fat mass. A loss of fat mass is associated with significant metabolic perturbations, all guaranteed to return the body to the higher fat mass. This includes physical changes, such as reductions in metabolic rate, thermogenesis, but also profound chemical changes, both within the adipocyte and brain. The adipocyte has long been considered a simple, inert storage vessel for fat. Recent research has demonstrated the adipocyte is an active synthetic site for numerous cytokines and other chemicals that have not only local metabolic effects, but also impact on numerous aspects of body function, from appetite regulation through to the timing of sexual maturity and fertility. When an adipocyte releases its fat content, a number of events are initiated that, in the long term, promote the restitution of fat to the adipocyte. If adhering to a programme restrictive diet and increased physical activity were not hard enough in our perpetual feast/sedentary society, human physiology plots against the obese individual. This framework is the strongest argument for the active prevention of obesity, especially in the absence of any effective "cures".

Endocrine problems such as hypothyroidism, and Cushing's syndrome can promote weight gain and should be considered in the clinical evaluation of the obese patient. Cushing's syndrome is however a rare cause of obesity.

Estimating the effect of environment

Twin research conducted at St Thomas' Hospital London and on the St Vincent's campus has estimated the effect of various environmental factors on total body and central abdominal fat. Use of the twin model provides a robust model for estimating environmental influence independent of genetic influences and other environmental factors. Using this model, we were able to show that physical activity was the strongest environmental influence on total and central abdominal fat.[2] Postmenopausal oestrogen replacement therapy and cigarette smoking were lesser influences[3] and no influence of dietary composition[4] was found in these cross-sectional studies of postmenopausal women.

Our group was the first to report a protective gene-environment interaction between physical activity and body fat mass. In those genetically predisposed to obesity a higher level of physical activity is associated with significantly lower fat measures, much greater an effect compared to those without any risk of obesity.[2] These findings suggest that higher levels of physical activity may be useful in preventing obesity in the genetically susceptible.

Current research we are undertaking on the St Vincent's campus, in collaboration with St Thomas' is currently examining for gene-environment interactions between body fat and other aspects of the metabolic syndrome (insulin resistance syndrome) and other lifestyle factors.

Management

The first step in starting a weight management regimen is to establish reasonable weight and life style targets. Patients often have unrealistic expectations of what is possible, given what is known about the genetics and physiology of obesity. The body mass index (weight divided by height squared) will indicate the degree of obesity. Cut-offs for the various levels of obesity are indicated in Table 1.

Group	BMI (kg/m2)
Healthy weight	20-24.9
Overweight	25.0-29.9
Obese	30.0-34.9
Morbidly obese	>35.0

Table 1. Classification for obesity using body mass index.

The basics in diet and exercise

The challenge in weight management is to guide the patient to effective, long term restructuring of their eating habits, food choices and physical activity.

Body weight is governed by the simple law of energy conservation, given some qualifying factors elaborated upon in the above. If energy intake exceeds energy output, there will be weight gain, and visa versa. The simplest means of reducing energy intake is to reduce the intake of energy dense foods, including high fat and high carbohydrate foods. Patients need to become savvy interpreters of food labels, especially newer "low-fat" foods, which can contain large amounts of sugars as substitutes for fat. Patients should eat more fibre-containing foods (such as vegetables and fruits), as well as lean protein foods (such as lean meat, chicken or fish). The most important concept is total caloric reduction, most easily achieved by fat and carbohydrate reduction. Many patients mistakenly fall into the trap of not considering carbohydrate calories however. High carbohydrate diets can promote weight gain or prevent weight loss if calories consumed exceed energy output. Of course, a reduction in alcohol calories will also help.

The assistance of a nutritionist experienced in weight reduction is an important starting point. There are also numerous ethical patient resources and information leaflets on nutrition available.

On the energy output side of the equation is physical activity. Any reduction in sedentariness is a starting point. Many mistakenly advise obese patients to undertake far too strenuous physical activity in the initial phases of weight reduction. The effort involved in walking on the flat for an overweight or obese individual is significantly greater than for a lean one. Swedish studies have demonstrated that overweight women walking 100m flat grade are working at 70 per cent of their maximal aerobic capacity, compared to 50 per cent when lean people jog. A suitable initial programme may suggest an increase in any walking activity in performing usual daily duties. Longer term a goal of at least 30 minutes walking daily is required, especially for weight maintenance.

Some patients will require specialised psychological assistance, including cognitive behavioural therapy or hypnotherapy.

Very low energy diets (VLED) promote rapid weight reduction through severe caloric restriction and should be used only under careful medical supervision. These diets replace meals with a vitamin-fortified milk protein-based drink and allow only starch-free vegetables and low calorie beverages. These diets are useful for the initial phase of treatment of morbidly obese individuals, or obese patients with significant co-morbidities who have had little success despite some lifestyle changes. These diets can produce electrolyte abnormalities, particularly in patients receiving antihypertensives or diuretics. Patients with diabetes may require medication adjustment. Such a diet is contraindicated in pregnancy.

Drugs

The therapeutic drug options in obesity are increasing. There are currently two drugs available for weight management: orlestat and sibutramine.

Orlestat is a pancreatic lipase inhibitor, reversibly inhibiting its hydrolytic activity on ingested fats and reducing intestinal fat absorption by 30 per cent. This medication can be a useful adjunct in association with a reduced fat, calorie restricted diet. Adverse effects include flatulence, bloating, loose or frequent motions, oily seepage.

Sibutramine is a centrally-acting serotonin and noradrenaline reuptake inhibitor which increases satiety and metabolic rate. Adverse effects include hypertension, flushing, headaches. Potentially dangerous interactions can occur with other drugs such as monoamine oxidase inhibitors and other antidepressants.

Surgery

Surgical approaches to weight reduction revolve around reducing consumption by limiting capacity (stomach stapling and, more recently, Lap-banding) or reducing absorption (intestinal bypass). There is significant evidence of comorbidity reduction with these techniques, as there is with any successful approach to weight reduction. These techniques could be considered in selected patients with significant comorbities who have been unable to reduce weight through other means.

Conclusions

Obesity has reached epidemic proportions in Australia. This will impact on almost every aspect of medicine and have consequences on the prevalence of diabetes, heart disease, hypertension and other related conditions. Health strategists are recognising the importance of the active prevention of obesity and there is a strong imperative for governments and community planners to build environments that promote activity (rather than prevent it). Research into the regulation of body fat is required to better understand the mechanisms that promote weight regain. Currently, achieving and maintaining healthy weight will rely on the changes individuals make and maintain in an otherwise obesogenic environment.

References

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2. Samaras K, Kelly PJ, Chiano MN, Spector TD, Campbell LV. Genetic and environmental influences on total and central abdominal fat: the effect of physical activity in female twins. Annals of Internal Medicine 1999; 130:873-882
3. Samaras K, Spector TD, Kelly PJ, Campbell LV. Tobacco smoking and estrogen replacement therapy are associated with lower total and central fat in monozygotic twins. Int J Obesity 1998;22:149-156.
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St Vincent's Clinic Foundation Research Grants 2003

LADIES' COMMITTEE SR MARY BERNICE AWARD 1 – $100,000
Prof Bruce Brew
The involvement of quinolinic acid and other tryptophan catabolites in the pathogenesis of Alzheimer's Disease.

LADIES' COMMITTEE SR MARY BERNICE AWARD 2 – $30,000
Dr Joanne Joseph
An evaluation of in-vivo platelet and monocyte activation in patients receiving standard compared to drug-elutine (sirolimus) stents for stable coronary artery disease.

LADIES' COMMITTEE SR MARY BERNICE AWARD 3 – $30,000
Prof Ken Ho
Anabolic hormones in the therapy of glucocorticoid-induced protein wasting.

K+A COLLINS CANCER RESEARCH GRANT – $50,000
Dr D Segara
Investigation of the WNT signalling pathway in the development and progression of pancreatic cancer.

DI BOYD CANCER RESEARCH GRANT – $20,000
Prof David Ma/Dr Helen Tao
Gene expression profiling may reflect the clinical outcome in selected haematological malignant diseases.

ANNUAL GRANTS
Dr Diane Fatkin – $20,000
Evaluation of early disease in familial dilated cardiomyopathy

Prof Terence Campbell – $20,000
Structure of the HERG K+ channel drug binding site

Dr Alan Meagher – $20,000
Analysis of the class II HLA binding specifications of the p53 vaccine (Pentrix™) peptides

Dr Nirmal Patel – $20,000
Inner ear neural stem cell transfer and neurotrophin-3 (NT3) production in the mouse model

TRAVELLING FELLOWSHIP GRANT –
Dr Andrew Biankin $10,000
Postdoctoral Fellow in pancreatic cancer under the supervision of Professor Steven Leach in the Division of Surgical Oncology at Johns-Hopkins University Hospital

Dr David Brown $10,000
Postdoctoral study in neuroimmunology with Dr Evan Snyder at Harvard Medical School, Boston. Research in the field of neuroimmunology, examining the function of macrophage inhibitory cytokine-1 (MIC-1) in the central nervous system

STUDENT RESEARCH GRANT – $3,000
Ms Lily Wang
Does quinolinic acid cause astrocyrte apoptosis?

TOTAL $333,000

Note: The Committee agreed to recommend the granting of 4 annual awards rather than 5 awards and to divert some of the award money to funding an additional Travelling Scholarship as it was felt that both recipients qualified equally for the grant.

Dr David Mann

Practical approach to weight reduction

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Introduction

There are as many diets as there are diseases associated with being over weight, yet over weight patients rarely are motivated to change their lifestyles to achieve weight loss. Often there is a resistance for people to follow weight reduction diets simply because diets are perceived to be complicated and difficult and, in many cases, this certainly is true. Added on top of this, weight loss is rarely long term and there is almost always a regaining of the lost weight.

A significant problem encountered by patients attempting weight reduction can be the impracticality of the diet. In some cases, the time required to prepare for the diet is prohibitive or the meals required on the diet may be unsuitable or repetitive. Some diets are extremely limiting in food selection. It may be that a person must change their meal patterns altogether or that the meals the individual eats may not conform to the rest of the family's meals. These are very real problems that deter any well meaning dieter.

These obstacles should not be looked upon as excuses for dieters to avoid the issues of weight loss but rather practical solutions should be formulated to open the way for the dieter to achieve their goals. Clearly, a more main stream, practical approach to weight reduction is needed.

The ideal approach should not only be a practical one but one that actually

teaches or reconditions the patient into a new habit with eating. Whilst most clinicians may be aware of this, very few know how to go about modifying a person's eating habits.

Within the scope of this article, I hope to highlight some approaches that I have taken in my practice that have proven to be successful with most patients. The format and presentation of this article may be somewhat unusual but I also hope to provide some real life examples that actually apply to patients.

The topics covered may be controversial and ideas may be novel however when taking a long term view to behavior modification the ideas and suggestions will be apparent.

Setting Goals

As clinicians, we are very quick to impress on patients the importance of the ideal weight or the correct body mass index (BMI). Whilst I fully agree with these standards, and these standards give a good guideline to work by, we must use these standards only as a guideline. It is extremely difficult to apply these standards to a real person. In addition, the patients in our clinics may be morbidly obese, that is greater than 20kg over weight and often much more. The ideal weight or the correct BMI seem so far away and unreachable that we may actually be discouraging our patients to achieve their goals.

I find that initially, not setting a goal allows the patient to be in a better frame of mind and allows them to focus more importantly on the issues of cooking and arranging for meals on the diet. Focusing their attention and effort in doing the correct style of cooking or to add extra flavors or put in some incidental exercises instead will give better weight loss results. If an aim has to be discussed, we should always aim for an initial modest weight loss such as 5 to 6kg. It should then be pointed out that after they have attained this level, they can set a new target. I also find that letting the patient take control of this target allows them to feel more in control of their diet and weight loss.

Counting Calories

Traditionally, numerous diets worked by having the dieter count calories, add up grams of fat intake or drink 2 litres of water or a range of other activities that are difficult to achieve in a normal working day. Should a dieter add up grams of fat intake each day? They firstly need to have a fat counter at hand all day, every day. The values of food consumed needs to be weighed or measured fairly accurately and then a search is undertaken for that food in the fat counter. This is then recorded and at the end of the day the total is calculated. This is far too time consuming and totally impractical for a full time worker. Most patients I find are fed up with this "paranoia" approach to dieting. These activities distract a dieter from thinking about other more important areas of their eating behavior which, if given more time to focus on, would give better overall results. Occasionally, I do recommend that patients purchase a fat counter but only to have a glance through to see the approximate level of fat in different foods.

I try always to keep the diet elements to the basics and any unnecessary requirements should be avoided. I find that the opposite of what some diets tend to do actually works better.

Establishing an Eating Pattern

There is a common belief that reducing the volume of food intake will assist in reducing weight. To a large extent this may be true, however, given the relatively free supply of food in our society, what actually happens is that a reduction in food intake will result in a feeling of hunger and this will result in subsequent over eating.

We have often seen patients who may be either too busy or short of time and miss breakfast. Often such patients will skip lunch or have a very small lunch. When such patients arrive home, their hunger is so fierce that they will go on a non-stop eating binge and, of course, often pick high calorie food.

This pattern of "dieting" is so common and only results in further weight gain. In addition, reducing food volume not only encourages poor eating habits but it may result in lowered self esteem for the patient who finds their attempt at weight loss is unsuccessful.

This type of patient needs a great deal of reassurance and encouragement for them to try establishing an even eating pattern. This can be done by providing some practical options. For example, instead of trying to have breakfast at home, I suggest to the patient to only ever have breakfast at work or on the way to work. They may bring a loaf of bread into work on Monday morning, keep it in the fridge and when they arrive at work each morning they put on some toast and make a cup of tea before they start work.

For lunch, where there is insufficient time to buy or make lunch, I recommend to patients who may be working near a milk bar or sandwich shop to arrange for a prepared and possibly even delivered lunch to avoid hunger.

There is then the difficulty of cooking. More and more I am seeing couples who both work (the "Double Income No Kids" category), arrive home late and do not have an opportunity of cooking each night. Instead, they buy take away food or simply dine out at restaurants. I direct their attention to cooking products such as Chicken Tonight Cooking Sauces (this is only one example of many more). These are sauces that are pre-made and only require the addition of meat/chicken/fish and some vegetables. The best part about these products is that almost all of them are very low fat and do not contain preservatives or other additives. There is a salt content, however the addition of meats and vegetables brings the salt to an acceptable level.

I also encourage patients to precook their meals using these types of products, so that on a Sunday afternoon a couple of hours in the kitchen means that they can cook all of next weeks meals in one go and that they will only need to microwave to reheat during the week. Hence, cutting down on cooking time and best of all cut out buying take away food.

The aim of providing patients with these suggestions is to make it possible for them not only to be able to follow a diet but also it gradually reconditions them into a good eating pattern again. A

regular eating pattern will be able to avoid hunger and hence food choices can be more appropriate.

Normal Times and Social Times

The affluent society in which we live allows us to have ample amounts of food, especially high calorie food, around us at all times. As living organisms, humans are instinctively driven to eat; our survival is based on our ability to have strong instincts to eat.

The following suggestion may sound unusual but I have used it in my practice for a long time and it has suited almost everyone. It is an extremely important part of my re-education process that I find other diets neglect.

All diets are quick to tell dieters the food to limit themselves to or point out all the bad foods that they must avoid. Very few diets actually teach people how to still make the most of those really enjoyable foods (including restaurant meals, drinking alcohol, oily foods, desserts, etc.) that we all want. Up to now dieters have achieved weight loss by withholding from enjoyment. Is it any wonder that people avoid dieting!

My recommendation is that we should be teaching people how to eat enjoyable foods but at a level which, when balanced with the low calorie foods, will either achieve weight loss or maintain a constant weight. Most patients' initial reaction is that this concept cannot be successful. We are so firmly conditioned that enjoyable foods should always be avoided, that any suggestion of giving in to pleasure makes us feel uneasy. Because everyone has a social life, everybody goes out to eat or drink in one way or another. It would be difficult to avoid or modify in any way these social occasions. My advice to patients is to learn to relax on these occasions and enjoy the variety of food and drinks that is available but to revert back to the diet immediately afterwards.

Some patients report that they feel so guilty they have deviated from the diet that they do not return to it. The defeated feeling takes over them so strongly that their self-esteem is severely badly affected and self-control is abandoned. As strange as it may seem, if the dieter learns to "let go" and enjoy these socials they will almost never cause any harm and will continue to lose weight on their normal diet.

Further, if we could condition ourselves to thinking that the "enjoyable foods" are reserved for when we should be having a good time, this will automatically reduce the frequency of the high calorie food intake and allows for easier weight control.

Accessible Food Products

Food or food products and ingredients that are suggested must always be available in supermarkets. Everyone goes to the supermarkets; not everyone will go to a health food store and not all health food stores carry the same products. Dieters are very quick to deviate off the diet if they find that their attempts at purchasing the right products cannot be achieved at the first attempt.

Fortunately, the food products and cooking ingredients that are available to us in the supermarkets are not only of good quality with respect to low fat content, but they are also of good quality with respect to taste and flavor. Whatever the products, the ease with which any individual is able to obtain these products is extremely important. It is counter-productive to recommend a product that patients could only obtain from a special shop that is only in some suburbs and only at certain times of the year.

I also often recommend the use of frozen meals either as an emergency meal or just a lazy night meal. There are now so many different brands and varieties to choose from and all very good quality, low in fat and excellent in flavor. Again, the aim of these types of products are to make the process of following a diet easier.

Reassurance and Moral Support

Many clinicians underestimate the value of moral support during a weight reduction diet. Female patients require a great deal of support by way of explaining about fluid retention and sweet cravings during monthly menstrual periods. Men require a great deal of support in respect of the change in size rather than the change in weight. Men with a higher per cent muscle content who are currently doing muscle-bulking exercises will lose weight very slowly on the scales but will very quickly change in size.

During a diet these problems need to be explained to dieters to ensure that their emotions do not divert in the wrong direction. In fact, general explanation of the physiological changes that takes place with the dieter's body during the diet helps to alleviate any worries or concerns that a dieter may have about their weight loss.

The reassurance is important to avoid patients having thoughts that their diet is not working and the explanations will help them to understand how their body works and how the body can respond to food. This type of information is helpful for patients to ultimately understand the whole picture to be able to control their weight long after they have finished losing weight.

Conclusion

Often, the task of following a diet seems so insurmountable that many dieters simply avoid the issue of weight loss or weight control. As clinicians, we must be able to take into consideration all aspects of dieting and the complexities involved to help the patient clear the way to achieving their goals. The above is only an example of some of the problems encountered by a dieter and hopefully some solutions to make their job a little easier.

The constraints of this article does not allow more in-depth discussions on many other aspects of dieting such as the relationship between emotions and eating behavior, the problems of the "picking" behavior and explanations to dieters as to why some diets are inappropriate.

Dr Paul R. Roy

The new era of coronary stenting and its development at St Vincent's

When John Morgan and I did the first coronary balloon angioplasty at St Vincent's in 1980 we never envisaged what would happen over the next 20 years. Then, every angioplasty was associated with an acute closure rate of about 5 per cent due to dissection. Urgent surgery for those patients was associated with a higher than normal cardiac surgical mortality. It was very disruptive and irritating for our surgical colleagues. The results of balloon angioplasty were limited in the 1980s by the rate of dissection and acute closure, by subacute closure, and long term by a restenosis rate of 25 – 30 per cent.

The first coronary stent was implanted by Puel in Montpellier, France in 1986. I attended the first live course in coronary stenting in Lausanne in 1987. Acute and subacute thrombosis during the course appeared to be a significant problem and when I returned to St Vincent's our initial enthusiasm for stenting was lukewarm. The stents that were used in the Lausanne course were Wallstents and they were not immediately made commercially available because of the worry of thrombosis.

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During the period 1990 – 1993 an improved stent, known as the Palmas Schatz Stent became available. These stents were hand crimped on to the balloon in the cardiac catheter laboratory. Though they were an improvement on the previous stents, occasionally the crimped stent came off the balloon before it was deployed in the coronary artery and this of course caused embolization of the stent to an unwanted site in the vascular tree.

A cumbersome balloon mounted stent, known as the Cook Stent also became available at this time and was shown to be useful, for bailout in acute dissection.[1] This stent was used here at St Vincent's in a live demonstration course in 1993.

During our live demonstration course in 1995, David Baron and I had the opportunity to be the first in this country to use a factory produced stent with the stent crimped onto the balloon in the production process, rather than crimped on by the operator in the catheter lab. This was known as the AVE Microstent and was the forerunner of many such balloon mounted stents.

In 1994 – 1995 the Stress and Benestent Studies[2] demonstrated a 30 per cent reduction in restenosis rates when stents were used in preference to 'plain old' balloon angioplasty.

A subsequent fall in restenosis rates to 15 – 20 per cent, lead gradually to widespread use of stents over the period 1995 – 2002. During this period stent technology advanced rapidly with smaller, more secure stents with very low crossing profiles, making it possible for these stents to be tracked down into smaller and more tortuous vessels than was previously possible.

Anticoagulation to prevent post stent thrombosis also changed and advanced during this period. Recent studies have demonstrated the effectiveness of Aspirin (which inhibits cyclo oxygenase and thus decreases prostaglandin and thromboxane formation) in combination with Clopidogrel (an ADP receptor antagonist) to protect against acute and subacute thrombosis.[3] These two drugs together block two important pathways for platelet aggregation but do not block platelet aggregation completely. If, during the course of a stenting procedure, there is a complex situation where there is a high risk of thrombosis we also have available 2 B 3 A inhibitors. These drugs inhibit platelet receptors and prevent platelets binding to fibrinogen to form a clot. When given intravenously they can totally block the platelet aggregation process.

By 2002 our major problems with coronary stenting were restenosis (15 – 20 per cent) and the inability to reopen some chronic total occlusions. Comparisons of stents versus bypass surgery for triple vessel disease have shown similar follow up death and myocardial infarct rates but a higher need for further procedures in the stent group. This of course has been due mostly to restenosis.[4]

A revolution in stent technology has occurred in the last two years effectively addressing the problem of restenosis.

Restenosis is a result of neointimal hyperplasia. This occurs when the usual healing process and re-endothelialization inside the stented segment of the artery goes 'overboard'. The process can be roughly compared to a keloid scarring effect.

Neointimal growth involves dedifferentiation of vascular smooth muscle cells from a contractile state to a secretory state leading to cellular proliferation, migration from the media into the intima and synthesis of intracellular matrix. The patho-physiology of restenosis consists of the complex interaction of cytokines and growth factors with cellular and acellular elements. Until now, blockade of any one factor has been insufficient to inhibit the restenosis cascade. Attention has now been focused on disrupting essential central cellular processes that would subsequently affect 'downstream' events that ultimately lead to restenosis.

A vast amount of creative energy has gone into the development of a drug coated stent which in early trials has reduced the restenosis rate to 1 – 3 per cent.

Initially the stainless steel struts of the stent made attachment of a drug difficult. A polymer was ultimately designed which was coated onto the stent, allowing application of a drug in such a way that the drug would 'elute' slowly from the stent over thirty days. The drug currently used is Sirolimus, an immunosuppressive agent widely used post organ transplantation. Rapamycin, its original name, was discovered in soil samples brought home by researchers from Easter Island (named by the Dutch on Easter Day 1722). Transplant immunologists, Randall Morris and Clare Gregory, at Stanford University, observed that transplanted rat hearts treated with Sirolimus had clean coronary arteries instead of the usual intimal thickening observed in the coronary arteries of transplanted hearts. With many steps in between and with collaboration between experts in both drug and device development, Johnson & Johnson produced the first Sirolimus Stent, i.e., a stent covered with a polymer from which the drug Sirolimus is released slowly into the local tissue over 30 days. The FIM (first in man) study of this stent was an open label study of 45 patients with both fast and slow release coating of the stent. At 12 months there was zero restenosis in either group.[5]

The Ravel Study was a double-blind randomized trial of a drug eluting stent versus a bare metal stent in 238 patients. There was again 0 per cent restenosis versus 26 per cent in the bare metal stent.[6]

In the Sirius Trial reported by Leon M. et al, at the TCT meeting in Washington in September 2002, 1,058 patients were randomized to Sirolimus or bare stent. These were a group of more difficult patients with diabetes, long lesions, previous angioplasty and surgery. The results were again outstanding, with a Sirolimus Stent restenosis rate of 3.2 per cent compared to 35.4 per cent in the bare stent.

In May 2002, at the World Congress of Cardiology Live Demonstration Course which took place here at St Vincent's, David Baron, David Muller, Stephanie Wilson and myself were the first in this country to obtain access to the Sirolimus drug coated stent. From May until December 2002, we implanted 215 Sirolimus stents at St Vincent's Clinic in a variety of low and high risk lesions. Only one patient has thus far presented with restenosis.

So far this is the first anti-proliferative intervention that we have had which dramatically improves patient outcomes. Sirolimus has a cytostatic mechanism of

action that leaves vessel cells healthy and viable without killing them. It permits natural and normal healing of the vessel wall and re-endothelialisation. It acts in the G phase of cell metabolism (Figure 1). This means that the Sirolimus causes cytotaxis but not cytotoxicity and allows the cell to recover in due course.

At this stage we have great expectations for improved patient outcomes with drug-eluting stents. We do, however, need to be cautious that this drug doesn't simply delay restenosis for a year or two. We need to wait for long term restenosis rates before we get too enthusiastic.

If it turns out to be as good as it appears, some of the classic 'enemies' of percutaneous intervention such as multivessel disease, left main stenosis, small diameter vessels, bifurcations and femoral and tibial arteries may well be conquered by drug-eluting stents, leaving chronic total occlusions as our major challenge and hence very few patients who will need bypass surgery.

We should all be very grateful for the enormous effort that has gone into overcoming the substantial challenges of developing such a clever device.

Our group here at St Vincent's recently began a world first trial of a new stent with a new drug coating which we hope will be a refinement of the already successful Sirolimus Stent.

Current work in progress in other places involves attempts to produce stents which may be able to carry several drugs as well as Rapamycin. Efforts are also in progress to produce biodegradable stents, which will also be able to carry drugs to a specific site. All of these things are going to lead to a great improvement in our ability to treat patients with vascular disease, not only in the coronaries, but in other vascular beds as well.

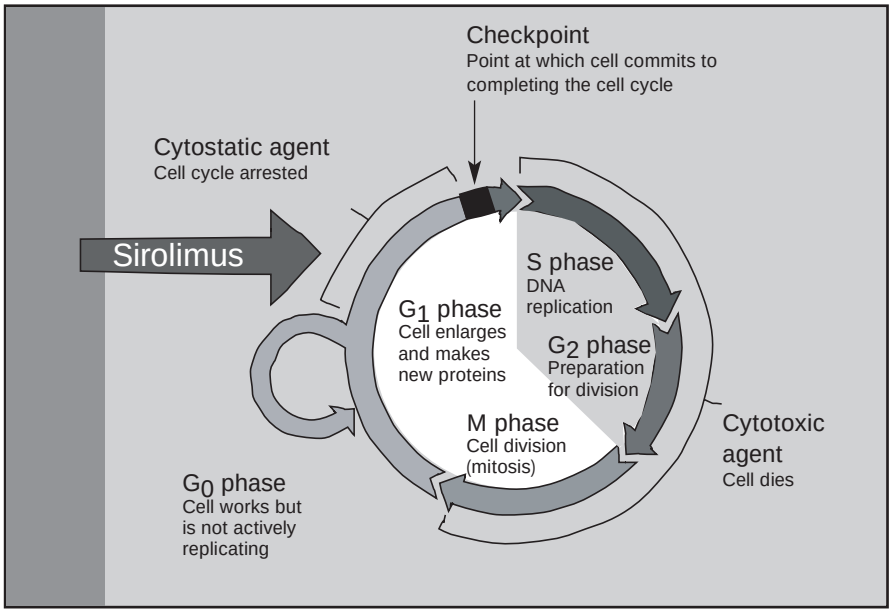

Figure 1:

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Dr David Williams

Endoscopic ultrasound – a new way of looking at the gastrointestinal tract

Introduction

Endoscopic ultrasound (EUS) is now an important diagnostic tool in the management of gastrointestinal diseases and, with refinements in technology, it has found diverse clinical applications. Whilst it is now widely adopted into clinical practice in USA, Japan and Europe, EUS is available in only a few centres in Australia. St Vincent's Hospital Campus has been providing an EUS service since 2000 and this article is intended to provide an overview of its current indications.

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Instruments

Endoscopic ultrasound (EUS) is performed with small high frequency ultrasound transducers mounted into the end of an endoscope, thereby producing clear and detailed images of the intestinal wall layer structure and surrounding organs. It is performed as an outpatient procedure under conscious sedation. No other current imaging method can reveal the gut wall from oesophagus to rectum as a series of histological correlates. With standard EUS frequencies of 5-30 MHz, the intestinal wall is imaged as a multi-layered structure, corresponding to mucosa, submucosa, muscularis and serosa respectively. This has tremendous relevance to GI cancer staging and determining the nature of submucosal lesions.

Several echoendoscopes are available, depending on the study required:

1. Radial scanner: The most widely used instrument is a mechanical driven radial scanner (7.5-20MHz) that provides a 360° view oriented perpendicular to the tip of the endoscope and allows detailed images of the intestinal wall and surrounding structures.
2. Linear Array scanner: This instrument provides 110° scanning in the same plane as the long axis of the endoscope and has colour Doppler capability. Therefore, this instrument allows real time EUS-guided needle biopsy through the intestinal wall of extraluminal lymph nodes and pancreas lesions, and underpins therapeutic applications such as endoscopic pancreatic pseudocyst drainage.
3. Catheter miniprobes: These small diameter, high frequency (20-30 MHz) probes can be passed down the channel of an endoscope and provide high resolution imaging of small mucosal lesions of the GI tract and bile duct.

Clinical Indications

Table 1 highlights the conditions in which EUS can make a difference with respect to clinical outcomes, and several of these indications are discussed in detail.

Staging GI Cancer

EUS is ideally suited to the TNM staging classification system of GI cancer, as it can not only define extent of tumour involvement through the gut wall but can also identify loco-regional nodal metastases and determine tumour vascular invasion (Figure 1). Since prognosis of such cancers correlates with stage at diagnosis, accurate pre-treatment staging is essential in treatment selection, avoidance of inappropriate surgery and determination of prognosis.

- Oesophageal cancer: *EUS is the best loco-regional staging modality for oesophageal cancer and is most useful where stage dependent treatment protocols are in place* (Figures 2 & 3). Numerous studies have demonstrated superiority of EUS compared with Computerised Tomography (CT), with reported T(umour) & N(odal) staging accuracy in the order of 90 per cent and 80 per cent respectively. A careful systematic review of the literature has reinforced this advantage.[1] Case series also demonstrate the ability of EUS to detect coeliac nodal and small liver metastases that are missed on CT, with consequent tumour upstaging and significant impact on patient management. EUS can also better define T4 disease (invasion of pleura, aorta, great vessels) that would prove not to be amenable to attempted resection.

Whilst well designed clinical trials have yet to fully establish the effect on clinical outcome, the increasing use of neoadjuvant chemoradio-

Table 1. When endoscopic ultrasound can make a difference

Cancer staging	Determine appropriate treatment (stage dependent protocols)
Oesophagus	Surgery (Stg I, IIA), neoadjuvant therapy (IIB, III), palliation (IV)
Stomach	Endoscopic mucosal resection (Stg 0,1), surgery (II, III)
Rectum	Local (Stg I) v. wide resection
EUS-guided tissue diagnosis	Mediastinal node cytology can preclude curative surgery in lung cancer
Submucosal lesions	Confirm and characterise endoscopic abnormalities Guide lesion management: excision v. observation
Pancreas	Confirm suspicious lesions on CT or MRI Localise small lesions Characterise cysts Stage pancreatic and ampullary cancer Evaluate for chronic pancreatitis
Biliary tree	Screen for CBD stones Detect cholangiocarcinoma and gallbladder cancer
EUS-guided therapy	Drainage pancreatic pseudocysts, coeliac plexus neurolysis

(Adapted from Lightdale C, Endoscopic ultrasound: when does it make a difference? Clinical Update American Society for GI Endoscopy 1999;6(4);1-4)

therapy places a higher value on pre-treatment staging. In patients undergoing surgery, an R0 resection (ie no residual disease in the area of primary tumour at end of operation) is associated with five year survival rates of 20-35 per cent as compared with R1/R2 resections (ie. residual microscopic/ macroscopic disease, 0-10 per cent five year survival). In a recent study, EUS correctly predicted tumour response to chemoradiation in 87 per cent patients who had tumour regression, with positive predictive value of 80 per cent.[2] As such EUS can be used to select patients who are likely to benefit from surgical resection after neoadjuvant therapy.

- Superficial GI cancers: EUS diagnosis of early GI tract malignancy is a recent and important development in endoscopy.

  a. Early oesophageal cancer: Because of screening programs on patients with Barrett's oesophagus, more cases of early oesophageal cancer are being recognised. High frequency catheter US probes can now improve the staging of early cancer over radial scanning instruments and can allow differentiation of tumour penetration to submucosa. Early cancers that do not penetrate into the submucosa can be treated with curative intent by using endoscopic mucosal resection (EMR) or mucosal ablation with argon plasma coagulation. In a large centre, EUS staging results were associated with a change of management plan in 40 per cent patients with Barrett's related early cancer and allowed for curative endoscopic treatments rather than oesoph-agectomy in selected cases.[3]

  b. Gastric cancer: As with the oesophagus, the evaluation of depth of cancer invasion is important in choosing preferable treatment such as EMR or surgical resection. For lesions that are confined to mucosa, EMR can be an effective treatment modality and if pathology confirms the EUS diagnosis, the patient is spared radical surgery.

  c. MALT lymphoma: Mucosa-associated lymphoid tissue (MALT) lymphoma is related to *Helicobacter pylori* infection. EUS staging can

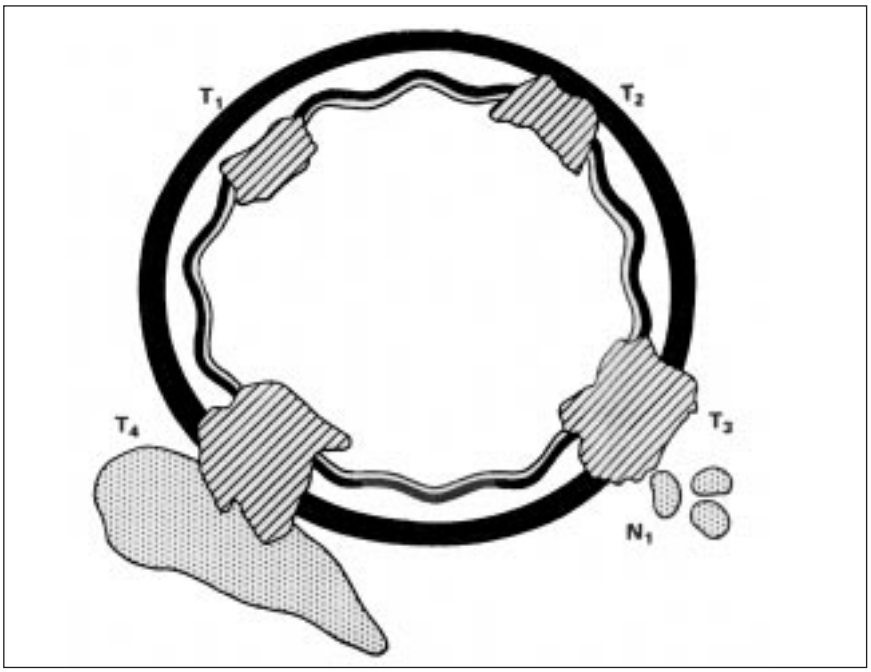

Figure 1: Diagrammatic representation of T and N staging of GI cancers based on layered structure of the gut wall as seen on EUS. T1, limited to mucosa/submucosa; T2, extending to muscularis; T3, extending beyond bowel wall; T4, invading adjacent structures

Figure 2: Oesophageal cancer, T1. A small hypoechoic tumour infiltrates into the echogenic submucosa but does not penetrate muscularis

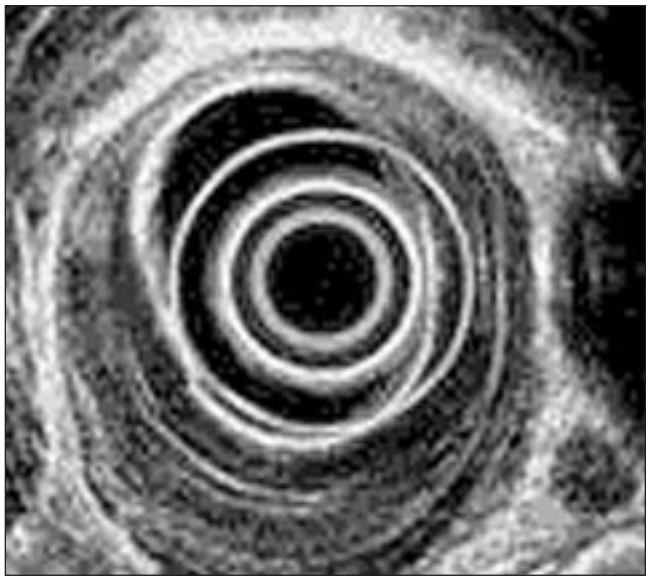

Figure 3: Oesophageal cancer, T3N1. An eccentric bulky tumour is seen extending through full thickness of the oesophageal wall. A small rounded malignant node is noted adjacent to the tumour.

predict response to therapy whereby disease limited to mucosa or submucosa is likely to regress after *H. pylori* eradication. In contrast, disease that penetrates to deeper layers will likely not regress and will require chemoradiation.

- Pancreatic cancer: The major challenge in evaluating patients with suspected pancreatic cancer is to best select those patients for potentially curative surgery or to identify those who will not benefit from surgical exploration. Despite advances in cross-sectional imaging (CT, MRI) that can now better define vascular invasion, EUS remains an important diagnostic tool (Figure 4). EUS can provide added accuracy in 1) patients with symptoms suggesting pancreatic disease but negative CT findings and in 2) patients with equivocal findings, even after triple phase multi-detector CT. *EUS is very sensitive for the detection of tumours <2cm in size and can reveal local nodal metastases not seen on other modalities.*[4] Cost-effectiveness studies have been uniformly positive when EUS is included in the staging algorithm for pancreas cancer, in that upstaging obviated unnecessary surgery and potential complications.[5]

- Pancreatic neuroendocrine tumours: Whilst surgical resection is usually the treatment of choice, it can be very difficult to localise these tumours pre-operatively or to determine disease extent. EUS is now regarded as a primary method of detecting neuroendocrine tumours as its sensitivity (up to 94 per cent in 1 series) is significantly higher than that of other imaging techniques (US, CT, MRI) and limits the need for more invasive investigations.[6] Somatostatin receptor scintigraphy is also a sensitive test for detection of gastrinoma, with the advantage of identifying metastases in the liver or outside the abdomen, but detects insulinoma less sensitively, as only 60 per cent of these tumours display somatostatin receptors. A large series investigating neuroendocrine tumours suggested that the best approach to tumour localisation was scintigraphy followed by EUS if the former was negative.[7]

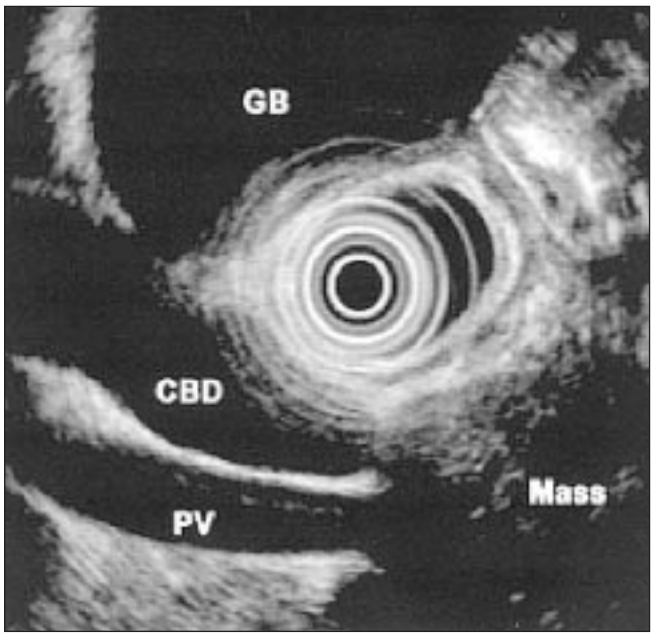

Figure 4: Pancreas cancer. EUS image of a mass in head of pancreas obstructing the bile and pancreatic ducts

- Rectal cancer: Endorectal EUS is an accurate method for evaluating local invasion of rectal cancer and perirectal lymph nodes, with T staging accuracy in the region of 85-90 per cent. As with oesophageal cancer, EUS is superior to CT in terms of T & N staging, although the main limitation is that tumours tend to be overstaged as it can be difficult to differentiate inflammatory changes from neoplastic tissue. Nonetheless, rectal EUS findings can determine the type of surgery (eg local excision for T1 disease v radical resection) as well as the use of pre-operative chemoradiation (T3-4, N1). It also has the ability to detect recurrent disease after surgical resection.

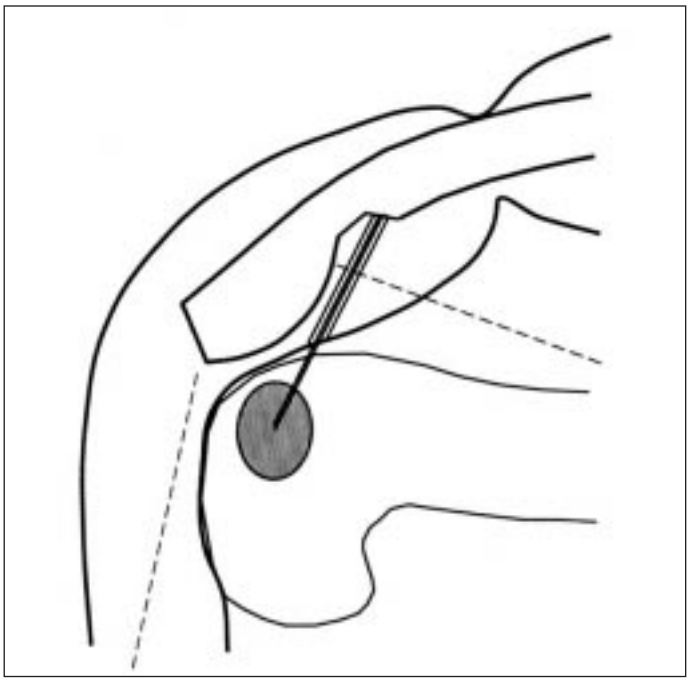

Figure 5: EUS-guided FNA biopsy of pancreas lesion using the linear scanner

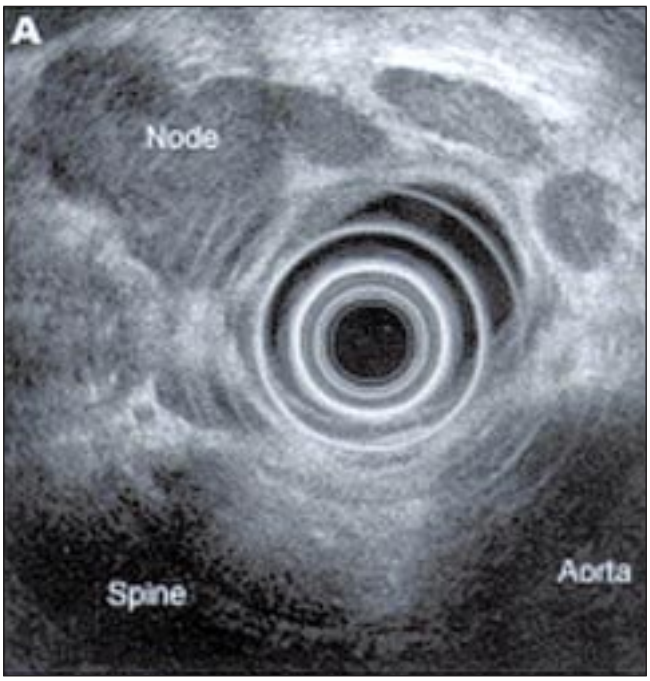

Figure 6A: EUS-guided FNA biopsy.

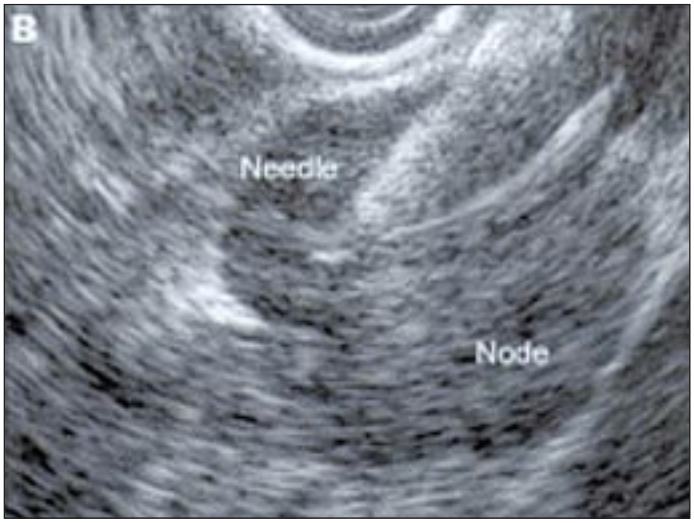

Figure 6B: Malignant appearing subcarinal adenopathy as seen on EUS in a patient with non-small cell lung cancer.

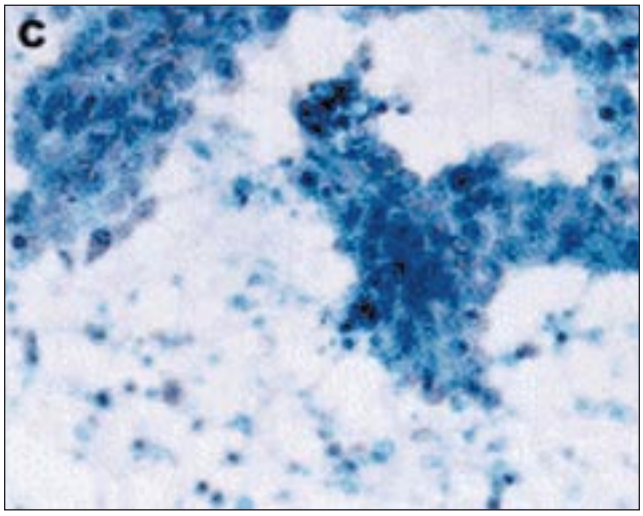

Figure 6C: EUS-guided FNA biopsy of subcarinal node. Nodal aspirate confirmed metastatic disease

EUS-Guided FNA Biopsy –

'Tissue is the issue'

Using the linear array scanner, precision needle placement under real time ultrasound guidance can be achieved (Figure 5). This enables the endoscopist to obtain samples from tissues away from the gut lumen, with current indications including sampling pancreas tumours, lymph nodes, submucosal lesions, ascites and liver metastases. It is a remarkably safe procedure with reported complication rates <1 per cent, related to infectious or bleeding events. Similarly the risk of malignant seeding is also exceedingly low.

Mediastinal staging of lung cancer

As per the American Joint Committee Cancer (AJCC) lung cancer staging classification, patients without mediastinal involvement are potential candidates for surgical resection, whereas patients with mediastinal invasion (T4) or contralateral mediastinal nodal disease (N2) are generally offered chemoradiation without surgery. The management of patients with ipsilateral mediastinal or subcarinal disease (N1) is perhaps more controversial but many centres would treat with chemo-radiotherapy.

CT scan has sensitivity and specificity only in the order of 70 per cent for detection of mediastinal disease. Bronchoscopy with transbronchial fine needle aspiration (FNA) also has sensitivity of 55-70 per cent, but cannot access the aortopulmonary window or inferior mediastinal nodes. Mediastinoscopy and thoracoscopy are costly and invasive. PET scanning has reported accuracy of 85 per cent but is limited by false negative results in tumours with low metabolic activity or nodes <1cm size.

EUS and EUS-guided FNA biopsy is an excellent modality for the posterior mediastinal staging of lung cancer and potentially may represent its widest use (Figure 6). EUS alone can identify malignant nodes readily in the posterior mediastinum based on morphological features but the addition of EUS-guided FNA biopsy improves both sensitivity

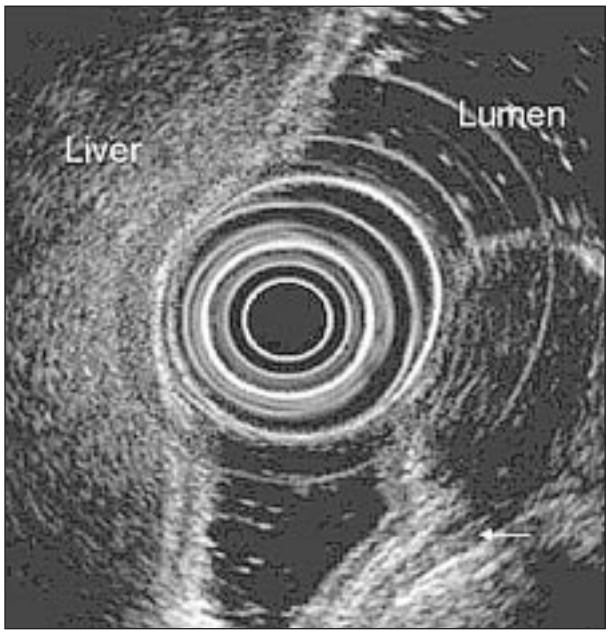

Figure 7: Gastrointestinal stromal tumour (GIST). EUS image of a gastric submucosal stromal tumour arising from the muscularis (4th layer).

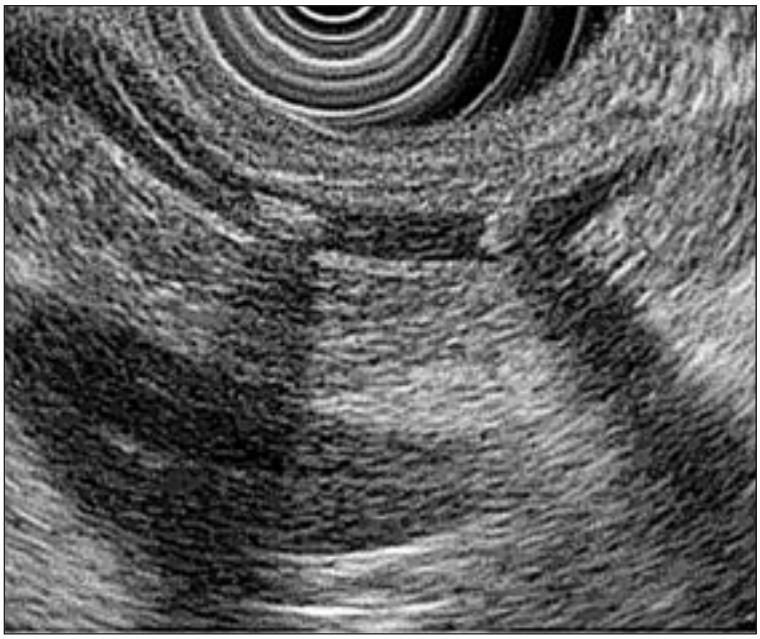

Figure 8: CBD stones. EUS image of 2 small calculi seen in a non-dilated common bile duct

and specificity for detection of malignant nodes. Several studies have confirmed its superiority to CT scan although there are no published studies comparing PET with EUS.[8] Nonetheless, outpatient EUS FNA is quick, safe and provides tissue for cytological analysis. Micrometastases can result in false negative EUS FNA because of the small number of cancer cells present. However, it is anticipated that developments in real time PCR techniques on nodal aspirates from EUS FNA may allow detection of micrometastases in pathologically benign nodes of patients with non-small cell lung cancer.

Submucosal Lesions

Intramural GI tumours arising below mucosa can present difficult management decisions. However, EUS can discriminate extramural compression from mural disease, has the ability to delineate the origin of tumours from within the wall layer structure and sonographic characteristics can confirm the pathological nature of the lesion. For example, lipomas are bright, echogenic tumours arising from the 3rd (submucosal) layer, whereas stromal tumours (GIST) are hypoechoic and usually emerge from the 4th (muscularis) layer (Figure 7). Sonographic features that arouse suspicion of malignant transformation of GIST tumours include size >3cm, irregular margins, internal cystic areas and peritumoural nodes.

Common Bile Duct Stones

EUS has high sensitivity and specificity for the detection of CBD stones, equal to or better than endoscopic retrograde cholangiopancreatography (ERCP), without the risk of ERCP-induced pancreatitis. This accuracy persists even for small stones in non-dilated ducts (Figure 8). In blinded comparative studies, ERCP sensitivity for stone detection was 79-90 per cent compared to 88-100 per cent for EUS.[9] False negative results for ERCP were caused by small stones in dilated ducts, a scenario in which EUS has excellent operating characteristics. In a follow-up study of 238 patients who were initially free of stones on EUS, 97 per cent had no biliary events after 12 months.[10] Therefore, when EUS is negative for CBD stones, ERCP or cholangiography can be avoided.

Prior to laparoscopic cholecystectomy for symptomatic cholelithiasis, EUS is best indicated in intermediate risk patients (ie. history of acute cholangitis or biliary pancreatitis; 8-10mm dilatation of CBD; unexplained anomalies in LFT's) where CBD stones are identified in 20-50 per cent of cases. When stones are confirmed there is the potential of performing ERCP and sphincterotomy at the same procedure. Equally, unsuspected lesions can be identified, such as gallbladder microlithiasis or pancreatoampullary tumours.

Therapeutic And Interventional EUS

EUS directed needle puncture offers a potentially expanding role for new endoscopic therapies, with reports of EUS-guided cholangiopancreatography and EUS-directed intratumoural injection therapy. Several established endoscopic treatments now incorporate EUS:

- Drainage of pancreatic pseudocysts: Endoscopic transgastric or transduodenal drainage can be achieved usually when a bulging lesion is seen at endoscopy, although there is risk of bleeding and perforation. EUS can determine optimal drainage site and prevent early complications by defining presence of intervening vessels, determine that the pseudocyst is not >1cm away from gut lumen (increased risk of perforation) and can characterise cyst contents (exclusion of cystic neoplasm or abscess). Using a dedicated large channel linear scanning echoendoscope cyst puncture and stent insertion can be achieved under direct US guidance.
- Coeliac plexus neurolysis(CPN): CPN has been used for many years to manage abdominal pain from

Table 2. Clinical application of EUS at St Vincent's Hospital Campus

INDICATION	No.
Cancer staging	
Oesophagus	64
Stomach	28
Rectum	14
Pancreas	49
Ampulla	31
Pancreas cyst	38
Pancreatic parenchyma	84
Submucosal lesions	96
CBD/Stone disease	58*
Neuroendocrine tumours	7
EUS-guided FNA	
Mediastinal nodes	7
Neuroendocrine tumour	1
Liver metastases	1
Coeliac axis mass	1

* CBD stones identified in 9 patients with normal transcutaneous US and cholangiography

advanced malignancy, using a surgical or transcutaneous approach. The coeliac axis is a landmark that is readily imaged by EUS via a transgastric approach. Wiersema reported EUS-guided transgastric CPN using absolute alcohol for patients with pancreatic cancer, showing significant reduction in pain scores that lasted 12 weeks in the absence of significant complications.[11]

EUS AT ST VINCENT'S HOSPITAL CAMPUS

EUS services are not well developed in Australia, hampered by high capital costs, the relative lack of stage dependent treatment protocols and the need for intensive training, even for experienced endoscopists. Nonetheless, St Vincent's Hospital Campus has been providing an endoscopic ultrasound service since 2000, with emphasis on GI cancer staging, evaluation of submucosal lesions, evaluation of pancreas parenchyma and exclusion of CBD stones. Table 2 highlights the EUS studies undertaken at St Vincent's Hospital since the service started to the present.

The technique of EUS-guided FNA biopsy has not been readily available, although has been able to provide cytological diagnoses when attempted (mediastinal nodal metastases in lung cancer, n=4; sarcoidosis, n=1; reactive mediastinal adenopathy, n=2; pancreatic neuroendocrine tumour, n=1; metastases left lobe liver in gastric cancer, n=1; metastatic SCC, n=1). However, a new linear scanner has now been acquired and it is anticipated that EUS-guided FNA biopsy can be more readily incorporated into diagnostic protocols, particularly for mediastinal staging of lung cancer.

SUMMARY

EUS has come of age as an endoscopic diagnostic modality. It allows clear examination of the gut wall for tumour invasion and can visualise and biopsy tissues adjacent to the intestinal tract such as lymph nodes and pancreas. As such, EUS has broad clinical applications and can enhance diagnosis, improve cancer staging and impact clinical decision making. Up until the present time, EUS has limited availability in Australia but the service is well established at St Vincent's Hospital and will continue to expand its utility.

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Dr Carolyn Bariol

Inflammatory Bowel Disease and St Vincent's experience with the use of Thalidomide

Introduction

Inflammatory Bowel Disease, including Crohn's Disease and Ulcerative Colitis, is a chronic inflammatory condition of the gastrointestinal tract. It affects an estimated 23,000 individuals in Australia and, although the overall mortality of those affected is no greater than that of the general population, it can have a dramatic impact on quality of life. Knowledge of the genetics and immuno-pathogenesis of the disease is growing. The use of immunomodulating therapies, such as Infliximab, has resulted in improved outcomes in a disease that has traditionally been difficult to treat.

A pilot study examining the use of thalidomide in inflammatory bowel disease at St Vincent's Campus has yielded encouraging results in both ulcerative colitis and Crohn's disease, and provides further insights into the pathogenesis of this complex condition.

Carolyn Bariol is a consultant gastroenterologist currently completing a research project into the genetics of colorectal cancer presursor lesions at St Vincent's Campus for the Faculty of Medicine, UNSW.

Epidemiology and Risk factors

Inflammatory bowel disease (IBD) can occur at any age but the peak incidence is 15-30 years with a second smaller peak at between 50 and 80 years. There is no gender specificity.

(A) Genetics

There is good evidence that genetic factors play a role in IBD. First-degree relatives are 3-20 times more likely to develop the disease than the background population. Twin studies suggest that there is higher concordance for Crohn's disease(CD) than ulcerative colitis(UC). Recent progress has been made in terms of identifying novel genetic markers of susceptibility to these conditions. Linkage analysis has established *CARD15/NOD2* as the first Crohn's disease susceptibility gene.[1] This gene is located on chromosome 16q12 and mutations have been observed in both familial and sporadic cases of the disease. cDNA nucleotide micorarrays or "DNA chip technologies" have identified a number of upregulated genes among individuals with ulcerative colitis including some pro-inflammatory cytokines and several HLA II transcripts.[2] Genetic mutations, however, do not adequately explain the development of CD or UC in the absence of environmental triggers.

(B) Environmental factors

Many environmental factors have been identified as contributing to the pathogenesis of IBD in susceptible individuals.

(i) Cigarette smoking

Studies have repeatedly shown a negative correlation for smoking and ulcerative colitis, and in contrast a positive correlation between smoking and Crohn's disease. In CD, smokers are more likely to have relapses, require corticosteroids and immunosuppressive therapies.[3] Those with UC who cease smoking have an increase in their disease activity.[4]

(ii) Infectious agents/Microorganisms

Exposure of the colonic mucosa to the faecal stream is a necessary requirement for development of IBD. This has been demonstrated in animal experiments where genetically susceptible mice raised in a germ-free environment do not develop the disease[5], and in human faecal diversion experiments. Various infectious agents are being actively pursued (Measles virus and Mycobacterium paratuberculosis) but to date a causative link remains unproven.

(iii) Appendicectomy

Studies suggest that childhood appendicectomy confers protection against the development of ulcerative colitis. Those who have had their appendix removed for an inflammatory indication before age 20 have a reduced risk of developing UC. The risk of developing Crohns's disease is unaltered.[6]

Pathogenesis

The pathogenesis of inflammatory bowel disease is the result of a dysregulation and upregulation of the normal immune responses to dietary and microbial antigens normally found in the intestinal lumen. Mucosal injury is the result of a multi-step process commencing with antigen presentation to CD4+ helper T lymphocytes. As the immune response is triggered, activated CD4+ T cells secrete cytokines, which in turn recruit and stimulate additional

immune cells, eventually leading to mucosal damage. Some of the immune abnormalities studied in inflammatory bowel disease are briefly mentioned below.

Leucocyte and epithelial responses

In terms of lymphocyte populations, an increase in T-cell proliferation and increased numbers of circulating B cells have been reported. Autoantibodies such as p-ANCA (increased in ulcerative colitis) and ASCA (anti-Saccharomyces cervisiae antibodies – increased in Crohn's disease) have been identified and may be useful in distinguishing the two diseases.[7] Enhanced expression of adhesion molecules and increased leucocyte binding to endothelial cells is also described, as are alterations in intestinal mucous and increased intestinal permeability.

Immunoregulatory and inflammatory cytokines

In Crohn's disease, Th1 cells (CD4+ helper cells that induce cell-mediated immunity) are upregulated. This results in increased secretion of the pro-inflammatory cytokines, TNFα and IFNγ. Other recently established pro-inflammatory cytokines with a role in the pathogenesis of IBD are IL-12, IL-16, IL-18, macrophage migration inhibiting factor (MIF) and transforming growth factor beta (TGFβ).

TREATMENTS

For many years, the treatment of inflammatory bowel disease has consisted of corticosteroids for acute exacerbations, 5-amino-salicylates as maintenance therapy for colonic disease, and steroid-sparing agents such as azathioprine for steroid dependent patients. IBD is a notoriously difficult condition to treat due to problems with drug toxicities, patient non-compliance and the cost of long-term therapies. The heterogeneity of disease and the need for tailored drug combinations have prevented the establishment of large controlled trials for standard therapies.

Our expanding knowledge about the immunopathogenesis of this disease has initiated the use of various immunomodulating therapies. The introduction of Infliximab, an intravenous chimeric anti-TNFα antibody (first used for Crohn's disease in 1998), brought extremely encouraging results in terms of disease remission and fistula closure although there were initial concerns regarding an increase in lymphoproliferative malignancies.

Thalidomide, which reduces the production of TNFα has been used on the St Vincent's Campus for several years in specialised settings such as aphthous ulceration in HIV patients and graft versus host disease in bone marrow transplantation. This knowledge and its application in Crohn's disease by Drs Antony Wettstein and Alan Meagher in 1996 led to an impressive longterm clinical remission in a women with chronic gastrointestinal haemorrhage requiring multiple transfusions and in whom all conventional treatment had failed. This novel use for thalidomide was subsequently reported in the Lancet[8] and an open-label pilot study was commenced soon after with the financial support of the St Vincent's Clinic Foundation. A summary of the publication[9] resulting from this study is set out below.

EARLY STUDIES ON THE SAFETY AND EFFICACY OF THALIDOMIDE FOR SYMPTOMATIC INFLAMMATORY BOWEL DISEASE

Thalidomide, α-N-phthalimido-glutarimide, was synthesized in 1956 and first used as a sedative and anti-emetic until foetal abnormalities resulted in the drug being withdrawn promptly from the market. Since then, ongoing clinical research has proven thalidomide to be effective in several inflammatory and immune-mediated conditions, including erythema nodosum leprosum(ENL), and Behcet's disease. Its effect may be due to inhibition of release of the cytokine, tumour necrosis factor alpha from activated inflammatory cells. Increased levels of inflammatory cytokines, including TNFα, have been isolated in the stools and intestinal mucosa of patients with Crohn's disease and ulcerative colitis. It may act by stimulating neutrophil accumulation, granuloma formation, upregulation of adhesion molecules on endothelium, and prothrombotic effects. Thalidomide reduces production of TNFα from stimulated monocytes in vitro in a dose-dependent fashion by enhancing the degradation of TNFα mRNA.

We have performed an open label study assessing the efficacy and safety of thalidomide for the treatment of chronic symptomatic inflammatory bowel disease.

Methods

Patients were eligible for this study if they had histologically proven inflammatory bowel disease for at least 6 months and were aged 16-80 years. Female patients were limited to those unable to conceive (post-menopausal, surgically sterilised or past hysterectomy). Male patients remained sexually abstinent or used barrier methods of contraception throughout the study period and for one month post-trial. Thalidomide was prescribed at a starting dose of 100mg and increased stepwise by 100mg to a maximum of 400mg per day according to the patients' symptoms and side effect profile. The treatment period was twelve weeks. Patients underwent a complete medical history and physical examination (including neurological assessment) prior to commencement of thalidomide, and then at weeks 2, 4, 8, and 12. Data recorded at each visit included stool frequency, and consistency, Crohn's disease activity index (CDAI), serum UEC, FBC, LFT, amylase, ESR and C reactive protein. Laboratory assays for TNFα, Il6 and Il8 were performed at weeks 0 and week 12. All patients underwent full colonoscopy at trial commencement and immediately post-trial. Macroscopic appearance and histology of biopsies were scored using previously described numerical systems. All patients underwent nerve conduction studies at cessation of the trial. Individuals were also reviewed 8-12 weeks after cessation of thalidomide to reassess stool frequency and consistency.

Results

Demographic data

Eleven patients were enrolled (9 male, 2 post-menopausal females , mean age 33, range 20-77). Six patients had CD, four UC, one indeterminate

Table 1 Clinical data

	Pretreatment	Week 12	p value
Clinical			
Stool frequency (no stools /day)	4.3 (2 -9)	2.3 (1-9)	0.0012
Stool consistency (1-3)	2.1 (1-3)	1.2 (1-2)	0.02
CDAI	117 (82-157)	48 (8-112)	0.0008
Endoscopic grade (0-3)	2.3 (2-3)	0.9 (0-3)	0.011
Histological grade (0-8)	5.9 (3-7)	3.8 (1-8)	0.03
Serology			
ESRmm/h	20.8 (2-50)	8.7 (2-18)	0.044
CRPmg/L	13.8 (1-32)	7.2 (1-21)	0.023
Il6 pg/mL	17.2 (1-54)	15 (1-60)	0.39
IL8 pg/mL	22.9 (1-89)	21.3 (3-76)	0.7
TNFa pg/mL	25.9 (2-48)	27.1 (4-40)	0.32

Results are expressed as mean(range)

colitis(IC). Seven patients were steroid dependent, five took azathioprine and all took 5-amino salicylate compounds in established doses.

Clinical data (see table 1)

Two patients with ulcerative colitis withdrew within three weeks of starting thalidomide due to intolerable mood disturbances. They were excluded from further analysis. Nine patients completed the study. Of these, eight experienced an improvement of stool frequency and stool consistency with thalidomide. One patient with CD did not respond. The median dose of thalidomide during the study was 100mg (range 100-400) and all responders completed the study at a dose of 100mg daily. At cessation of the trial, four patients had completely healed mucosa and three had a reduction in inflammation.

Comparative biopsies before and after treatment were assessed. In those who had pre- and post-treatment biopsies, there was a significant reduction in inflammatory grade.

Laboratory data

With thalidomide there was a significant reduction in C reactive protein and ESR. CDAI improved from a mean of 117 to 48. The assays for serum TNFα demonstrated no significant difference.

Nerve conduction studies performed post-trial showed minor abnormalities in the sensory action potential and motor conduction velocity in the right ulnar and common peroneal nerve of one patient. The clinical importance of these results are uncertain. He remains asymptomatic.

Post-trial clinical data

Stool frequency returned to approximate pre-trial levels in all patients 8-12 weeks following cessation of thalidomide (mean 2.3 to 4.4 stools/day, p 0.005)

Discussion

This study strongly suggests that thalidomide is effective as short term therapy in symptomatic inflammatory bowel disease. A significant clinical response in eight of nine patients who completed three months of therapy was observed. Symptomatic improvement was noted with stool frequency decreasing from 4.3 to 2.3 motions per day. The clinical findings were supported by improvement in colonoscopic and histological features and the reduction in laboratory markers of inflammation. On review two months post-trial, the stool frequency returned to pre-treatment levels indicating that the effect of thalidomide is of short term duration.

Two similar open-labelled studies have revealed promising results in Crohn's disease patients treated with thalidomide for moderate to severely active disease. The first described a 56 per cent response rate and 33 per cent remission rate in luminal disease after 12 weeks[10] and the second a 70 per cent response rate and 20 per cent remission rate after 12 weeks.[11] Both used CDAI reduction alone as their criteria for response. The side effect profiles were very similar to our own, however there was no data on maintenance of response once thalidomide was ceased.

The short term nature of the thalidomide response noted in our study is of concern, and longer term studies with screening for neuropathy are needed. Minimizing the dose over an extended period is a potential solution. The initial case reported by our group has been relapse-free on a total weekly thalidomide dose of 100mg. In time, the identification of a less toxic thalidomide molecule such as CC-3052[12] may enable safe use of a non-neurotoxic, non-teratogenic, anti-inflammatory agent for inflammatory bowel disease.

The side effects of thalidomide cannot be overemphasized, particularly teratogenicity and peripheral neuropathy. The incidence of peripheral neuropathy is related to dose, with most cases of neuropathy occurring after 40 to 50g. One study showed that 0.5 per cent of patients who received thalidomide developed a painful peripheral neuropathy. This may be irreversible in about fifty per cent of patients.[13] Careful

monitoring of all patients treated with thalidomide is advised using nerve conduction studies. Minor adverse effects in this study were well tolerated. Night sedation was considered an advantage by some patients.

TNFα is released by activated inflammatory cells and is responsible in part for the immune reactions producing enterocolonic inflammation. The effect of thalidomide may be demonstrated in this study by the reduction of other inflammatory markers including ESR and CRP. However, the serum levels of TNFα did not decrease in this study over a three month period. Other possible mechanisms of action of thalidomide may account for the lack of serum TNFα response, including inhibition of angiogenesis induced by basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Specific immunostaining for TNFα at the mucosal level would help determine its role in the mechanism of action of thalidomide in inflammatory bowel disease.

Future trials are needed to measure the effect of thalidomide on local release of colonic TNFα. Studies of clinical response with infusion of anti-TNFα antibody in Crohn's disease have been marked by concerns of lymphomatous transformation, reactivation of tuberculosis[14] and the development of human anti-chimeric antibodies. The encouraging results of this study suggest that thalidomide may provide an effective oral alternative to intravenous monoclonal chimeric anti-TNFα antibody.

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Table 2 Adverse reactions

Symptom	number
Sedation	11
Xerostomia	11
Skin dryness	6
Mood disturbance	2
Constipation	3
Deep venous thrombosis	1
Loss of libido	1

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State of the art in Cochlear Implantation

Introduction

A cochlear implant is an electronic device surgically implanted in the skull that provides auditory sensation by direct stimulation of the cochlear nerve. This technology allows for the restoration of hearing in selected patients with either a congenital or acquired sensorineural hearing loss.

Dr John Tonkin of St Vincent's Hospital, Sydney, implanted the first cochlear implant device in Australia in 1977.[1] Professor Graeme Clark of Melbourne implanted Australia's first multi-channel cochlear implant device in 1978. Multi-channel cochlear implants first gained Food and Drug Administration clearance in the United States for adults in 1985 and for children in 1990. Many of the recent advances in the field of cochlear implantation have taken place in Australia. St Vincent's Hospital, Sydney, has played a cardinal role in the research and development of auditory implantation technology particularly in the realm of auditory brainstem implantation.

Over the last five years there have been dramatic advances in the software and hardware of cochlear implants together with improved surgical techniques. This has led to a significant widening of the candidacy of patients who could potentially benefit from their use.

Dr Phillip Chang

Cochlear implant design

The hardware of the cochlear implant consists of both an external and implantable component (Figure 1). The software consists of various strategies utilised to process and deliver auditory information to the auditory system.

The externally worn component of the cochlear implant is presently contained entirely behind the ear (Figures 2 and 3). It contains an ear level microphone, a speech processor,

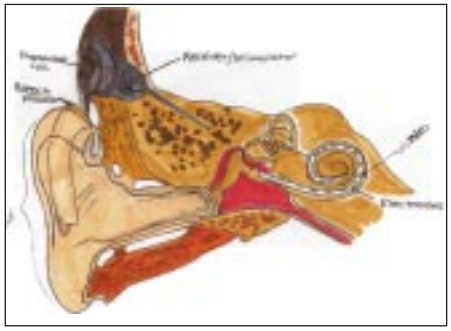

Figure 1: Cochlear implant consists of an external component worn behind the ear and an internal component embedded within the temporal bone. The electrode is introduced into the cochlea.

Figure 2: External component of the cochlear implant – Superseded larger body-worn device.

Figure 3: External component of the cochlear implant – Newer smaller ear-level device.

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Figure 4: The internal portion of the cochlear implant is seated within the thickness of the cranial vault and has both a cochlear and a ball electrode.

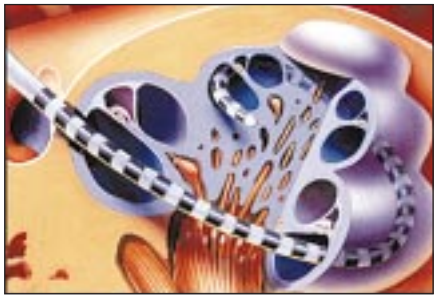

Figure 5: The electrode of the implant lies within the lumen of the cochlea and directly stimulates the cochlear nerve within the core or modiolus of the cochlea. The damaged inner ear hair cells are therefore bypassed.

Figure 6: The most advanced cochlear implant has a pre-curled electrode permitting it to lie closer to the cochlear nerve.

and an electromagnetic transmitter. In addition the batteries are contained within the external part of the implant.

The implanted internal component lies within a bony seat created within the thickness of the cranial vault postero-superior to the auricle (Figure 4). This component consists of a subcutaneous receiver coil, a microprocessor based stimulator, and the electrode wire that is inserted into the cochlea (Figure 5).

The cochlear implant works by virtue of a microphone that picks up speech and environmental sounds. These are filtered, analysed and digitised into coded signals by the speech processor within the external device. The signals are sent from the speech processor to the transmitting magnetic coil. The coil sends these signals as FM signals across the intact scalp from the external to the internal component.

The internal portion of the implant device has a magnetic disk which serves as the receiver of the signal. This information passes to the internal stimulator and then to the electrode array. By a series of electrical impulses the array directly stimulates the cochlear nerve situated in the bony core or the modiolus of the cochlea. The sound information is subsequently sent along the cochlear nerve to the higher centers of the brain for interpretation.

The cochlear implant has a speech processor that has the ability to utilise more than one software strategy in order to process sound. This allows optimal digital processing of environmental and speech sounds. Different strategies emphasize different pitch, loudness and timing cues. Cochlear implant recipients can therefore choose a certain quality of auditory perception when listening to particular sounds in particular environments. This advance permits improved speech perception and sound appreciation (e.g. music).

Recent Advances

Over the last 30 years there has been a dramatic decrease in the size of both the external and internal hardware components of the cochlear implant.

In the early days of cochlear implantation the external component was literally the size of a briefcase. The external portion is now available as an ear level device smaller in size than a conventional hearing aid. The smaller size of the device facilitates easier use and mobility for patients.

The internal implantable receiver/stimulator is also smaller permitting insertion via smaller incisions. This is a particular advantage in the implantation of younger infants. A smaller internal device also minimises its extrusion and inadvertent trauma.

Cochlear implant devices in their technological infancy had only one electrode with which to stimulate the cochlear nerve. Multi-channel devices now consist of up to 22 sites of stimulation along the electrode. This allows excitation along the whole length of the cochlear nerve within the cochlea. By doing so the frequency-recognition or tonotopical arrangement of auditory stimulation is maintained. Delivery of superior stimulation to the central nervous system has led to improved auditory sensation for implanted patients.

Over recent years there have been significant advances in electrode design. The ideal position of the electrode within the lumen of the cochlea is against its inner wall so that it lies as close as possible to the cochlear nerve within the core or modiolus of the cochlea. In such a position the implant requires less energy to stimulate the cochlear nerve, battery life is longer and there is less “cross talk” between each of the 22 stimulation sites. To achieve this electrode position the latest electrode has a preformed curl held straight with a stylet (Figure 6). Following insertion of the electrode into the cochlea the stylet is removed and the electrode gently curls and intimately embraces the cochlear nerve.

Surgery

The procedure for insertion of the cochlear implant is performed in sterile conditions under a general anaesthetic. It takes approximately two hours.

A small incision is made within a skin crease behind the ear (Figure 7). A pocket is created beneath the skin and muscle for the internal portion of the implant as it sits in a bony seat drilled within the thickness of the skull. It is held in position by sutures which pass through tiny separate holes drilled in the cranial vault.

The middle ear is accessed by the removal of the bone of the mastoid behind the ear via a limited mastoidectomy. The facial nerve is identified in its course through the temporal bone and a slot is created adjacent to this in order to enter the middle ear cavity.

Within the middle ear cavity the round window marks the entrance to the cochlea. The electrode is inserted through the enlarged round window and passed round the two and a half turns of the cochlea. A free muscle graft is placed around the electrode to create a seal at the round window thereby separating the potentially unclean middle ear from the sterile inner ear.

With the electrode in place and the rest of the internal component of the implant seated and fixed the overlying soft tissue is closed in layers. A head bandage is placed.

On the first post-operative day the head dressing is removed prior to the patient's discharge. Oral analgesics may be required for the first two days following surgery.

Complications

With current surgical techniques and technology complications associated with cochlear implantation are uncommon.[2] Damage to the facial nerve is possible but exceedingly uncommon. Risk of damage to the facial nerve is higher in cases of inner ear malformation as the facial nerve may lie in a more unpredictable position. Cerebrospinal leakage can occur either through the cochlea or the through the bony well created for the internal component. Device migration, extrusion or failure is very rare. The implanted patient is at no increased risk for meningitis with the implant devices currently available in Australia.

Switch On and Programming of the Implant

The device is switched on and programmed by a trained audiologist two to three weeks following surgery. This allows time for the wound to heal and the mild soft tissue swelling to settle. The cochlear implant is connected directly to a lap-top computer via a magnetic coil for programming. Each of the 22 sites of stimulation of the electrode in the cochlea is programmed in turn. Both a *threshold level and a comfortable loudness level* are programmed into the device using either behavioural or objective responses from the patient.

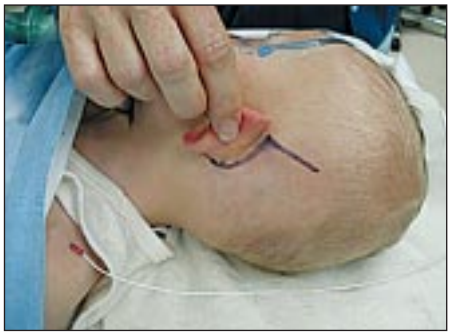

Figure 7: The cochlear implant is inserted via a small post-auricular incision.

As the patient becomes familiar with the implant through its use over the ensuing weeks, the programming of the cochlear implant is refined to attain the best sound quality for the patient. The switch-on is potentially an emotional event for patients as they experience the sensation of sound either for the first time or after being deprived of sound for years. Adequate and appropriate counselling about expectation is critical. At the time of switch-on patients often initially describe speech with the implant as having an electronic or robot-like quality. With time and use the quality of audition rapidly approaches that of natural and normal hearing.

Candidacy

Cochlear implants provide a means by which the sensation of hearing can be offered to patients with a sensorineural hearing loss who receive minimal benefit from hearing aids. The candidacy for cochlear implantation has dramatically widened over the last five years with broadening age and audiological criteria.

Age: The minimum age for cochlear implantation continues to decrease and is presently under the age of one year. By virtue of neural plasticity central auditory pathways develop in the first six years of life in response to auditory stimulation with the development occurring particularly rapidly within the first three years of life.

Most children implanted at an appropriate early age develop speech and language skills at the same rate as their hearing peers. In general they are able to attend mainstream schooling without additional tutelage.

Figure 8: Wider candidacy for cochlear implantation means that there is presently no minimum or maximum age criterion.

The cochlea is adult size at birth and therefore the size of the electrode of the cochlear implant is standard. The smaller implantable component presently available facilitates surgery on younger infants.

At the other end of the age spectrum there is no maximum age for implantation. The elderly are able to benefit from cochlear implantation equally as well as younger implantees (Figure 8).

Level of Hearing Loss: As the performance of cochlear implants has improved, the audiological criteria have widened to include patients with greater residual hearing. Formerly only those patients with a profound deafness were considered candidates for implantation. Currently those patients with severe hearing losses (~70dB HL) and who have limited benefit from hearing aid use are being considered for cochlear implantation.

Aetiology of Deafness: Severe congenital malformations (such as cochlear aplasia or the absence of the cochlear nerve) preclude cochlear implantation. Meningitis as a cause of deafness necessitates the early consideration of cochlear implantation. An early sequela of meningitis is ossification of the cochlea. Extensive ossification of the cochlea lumen contraindicates cochlear implantation. Limited ossification of the cochlea lumen can be overcome by further widening the entrance to the cochlea or a more extensive drill out of the cochlea. Aside from inner ear malformations and

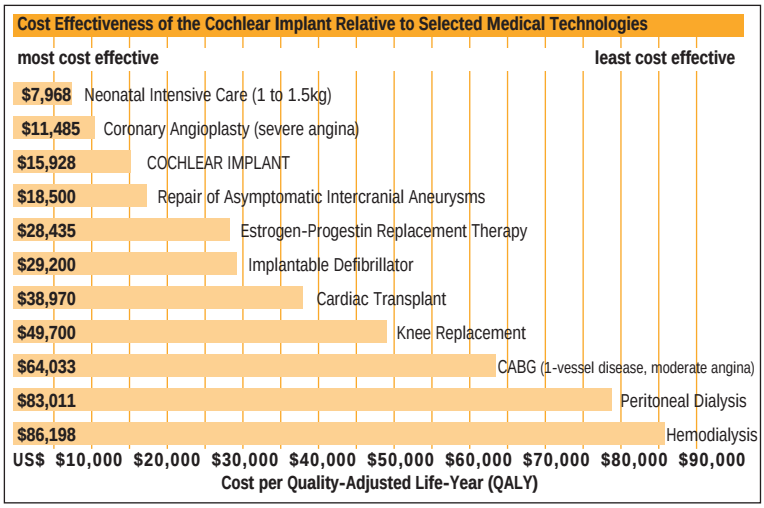

Figure 9: The cochlear implant represents one of the most cost-effective medical interventions.

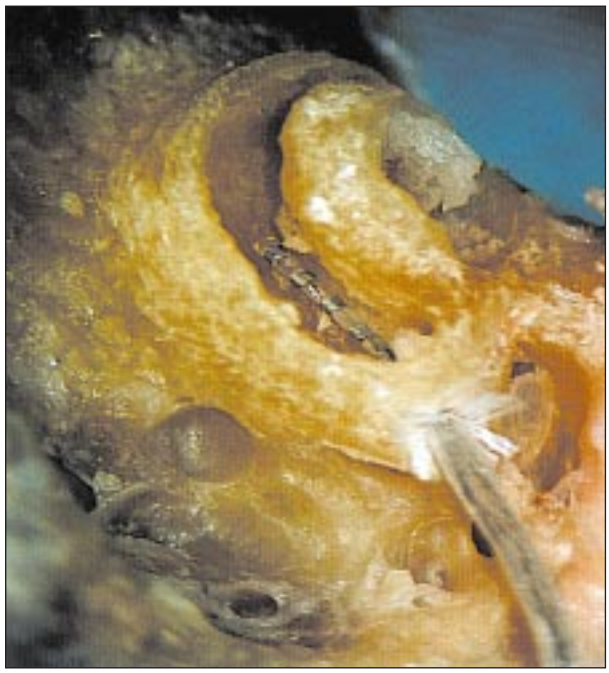

Figure 10: An experimental partially-inserted cochlear implant device is under trial. The device is seen partially inserted into the outer turns of a cadaveric cochlea.

meningitis the results from cochlear implantation are independent of the aetiology of the sensorineural hearing loss. Most sensorineural losses are the end result of loss of the hair cells in the cochlea leaving the spiral ganglion of the cochlear nerve intact and amenable to stimulation by cochlear implantation.

Other disabilities: Patients with cognitive, motor and other sensory disabilities can presently benefit from cochlear implantation. Each of these cases is fully assessed on an individual basis by the cochlear implant team. Patients must be able to tolerate a general anaesthetic, have an appropriate level of expectation and be motivated in the rehabilitation required.

Investigations

Each patient considered for a cochlear implant undergoes a comprehensive candidacy assessment. This includes a medical, audiological and psychosocial evaluation.

The medical assessment includes both a clinical and radiological examination. CT scanning of the temporal bones is performed to determine mastoid aeration, position of the facial nerve, development and patency of the cochlea. MR imaging is used to exclude a retro-cochlear cause for the hearing impairment, a contraindication for cochlear implantation.

Audiological testing is based on both behavioural and objective testing. Subjective testing may be difficult in infants and developmentally delayed patients. In these patients reliable objective testing in the form of automated brainstem response audiology, evoked cochleography and otoacoustic emissions is essential.

All patients are fully assessed from a psychosocial point of view to ensure that expectation of the implantee is realistic and that there is a necessary degree of dedication to the rehabilitation required. This applies to both adult and paediatric patients.

Benefit

There is presently no other technology that is even comparable to cochlear implantation in being able to replicate any of the other human senses. This technology has the ability to provide the sensation of hearing to a level and quality comparable to normal and natural hearing in selected patients.

Cochlear implants are among the most highly cost-effective medical technologies available (Figure 9). Benefits have also been shown in the quality of life, improved mental health, added safety and education, increased independence and improved job opportunities.[3]

Adult patients who have hearing loss that has occurred following the acquisition of speech and language (post-lingual hearing impaired) perform exceedingly well. In general these patients are able to detect all audible environmental sounds and speech. Most understand speech through audition alone without the assistance of lip-reading and are therefore able to use the telephone. Pre-lingually hearing impaired adults generally have more limited improvement in speech perception, but can benefit from improved perception of environmental sounds.

In the case of infants with hearing impairment the earlier a child is identified with a hearing impairment and is implanted the better that child will perform. Infants implanted at an appropriately early age develop normal or near-normal language and speech. The sensation of hearing with a cochlear implant is adopted as the natural hearing of these children. Up to 80 per cent of those infants implanted early achieve word recognition with out any other cues (open-set word recognition).[4] Optimal results of cochlear implantation in infants rely on early training with an auditory-verbal rehabilitation programme.

Favourable factors for cochlear implantation are young age at implantation, short duration of deafness, greater residual hearing, post-lingual deafness, and an acquired rather than a congenital hearing loss. Consistent use of the device, an educational environment, and social or family support are also helpful positive factors.

Future Directions

In years to come the hardware and software will continue to improve resulting in even better functional outcomes for implanted patients. Bilateral cochlear implants will potentially improve speech perception in noise and allow for the localization of sound. Prototypes of the totally implantable cochlear implants (TICI) with no external components have been developed. This will have a significant advantage from a cosmetic, comfort and convenience point of view.

Another advance on the horizon is a hybrid electro-acoustical stimulator (Figure 10). A short atraumatic electrode array is presently being trialled. It is partially inserted into the cochlea whereby only stimulating that portion of the cochlea that codes for higher frequencies. This will be suitable for high frequency hearing losses such as those secondary to presbyacusis, noise-induced hearing loss and ototoxicity.

By far the greatest advance in the future related to sensorineural hearing loss will be the time when cochlear implant technology will be obsolete. At this time damage to inner ear hair cells will be either avoided by genetic engineering or repaired with neural regeneration. Until this time cochlear implant technology will continue to serve to restore the sensation of hearing to adults and children alike.

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The Mission of St Vincent's Clinic Foundation

The people of Sydney and beyond are fortunate to benefit from one of the most comprehensive health care services available at the St Vincent's Campus at Darlinghurst. These facilities are part of the health and aged care facilities under the direction of the Sisters of Charity of Australia.

Integral to the Darlinghurst campus is the services and facilities provided by St Vincent's Clinic and St Vincent's Clinic Foundation. The aims of St Vincent's Clinic and St Vincent's Clinic Foundation are patient care, medical teaching and clinical research. The three aims are interlinked and each serves to strengthen the others.

Established in 1992, St Vincent's Clinic Foundation provides funds and support for medical research into matters of clinical significance as well as providing support for public and medical education.

Every advance in medical science has started with a commitment by a medical practitioner or a scientist to alleviating the pain and suffering of mankind.

Australia is rich in research bodies which focuses on clinical laboratory based research. However, funding is sparse for research conducted in the course of patient care. This where St Vincent's Clinic Foundation can focus some of the community's goodwill.

Since 1992, the Foundation has spent over $3.5 million and provided financial support for over 115 research projects. The Foundation has successfully supported vital research into disease and illness including cancer, diabetes, kidney disease, heart disease, arthritis, asthma, pulmonary disease, liver disease, pain, mental health, youth suicide, deep vein thrombosis, obesity, Alzheimer's Disease and adult stem cell research. Additionally the Foundation supports research into the function of genes and cells in many diseases. The Foundation also provides financial support for medical students who wish to undertake research during their study as well as a travelling scholarship providing support for a researcher studying overseas.

The Foundation depends on donations to continue to support this important research. We need your support to assist St Vincent's Clinic Foundation to continue to provide financial support to our researchers.

P.M. Valente

Acoustic Neuroma: Pneumocephalous, a rare complication

Introduction

The term acoustic neuroma (AN) is something of a misnomer, for this tumour is neither a neuroma nor acoustic, but rather correctly known as a Vestibular Schwannoma (VS)[1]. Its origin is from the sheath of Schwann cells (neurilemma) of the VIII nerve, in the region of the transition zone between the central and peripheral myelin, also known as the Obersteiner-Redlich zone.[2] The management of VS still presents significant difficulties despite modern investigations such as computer tomography (CT), magnetic resonance imaging (MRI), the operating microscope[3], facial nerve monitoring[4] and modern techniques of tumour excision.

Major complications (Table 1) still occur occasionally but only the minor complications occur with any frequency[5]. A rare complication of acoustic neuroma surgery is acute pneumocephalous. A patent extracranial to intracranial communication and a driving pressure for air flow through this communication must be present for ambient air to enter the cranial vault. Several conditions meet these criteria and predispose to the postoperative development of pneumocephalous.[6] A review of the St. Vincents Private Hospital, Sydney (SVPH) experience and a detailed report of a case are presented.

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Case Report

A 49 year-old man presented with a left sided hearing deficit due to an acoustic neuroma (Figure 1a-b). It measured 14mm in the coronal plane, 10mm antero-posterior and 8mm craniocaudal and extended into the cerebellopontine angle medially and to the fundus of the internal auditory canal laterally. A middle-fossa approach was undertaken in order to preserve hearing. Prior to closure of the craniotomy flap, a suction drain with multiple side holes was inserted.

On the first morning post-surgery the patient sat up suddenly and thereafter suffered a progressive loss of consciousness. It is believed that this suction drain became partially dislodged at the time the patient increased his intracranial pressure upon sitting up in bed. CT (Figure 2a-d) revealed the cause, a collection of gas over the frontal lobes. The suction drain was removed and the patient treated with 100 per cent oxygen. Thereafter he made a slow but uneventful recovery with full hearing and facial nerve function.

Discussion

Acoustic neuromas account for 78 per cent of all tumours of the cerebellopontine angle.[7] They are usually unilateral (sporadic form), although bilateral lesions may be noted as in Von Recklinghausen's Disease (Neurofibro-matosis Type-II form). The tumour most often presents symptomatically between the ages of 30 and 40 years, with a female to male predilection of 3 to 2. The size of the tumours ranges up to 5.0cm, although more commonly the size outside the canal is about 2.5 to 3.0cm.[8] It is important for the clinician to be aware that there is a remarkable degree of variability in the manifestations of these tumors.[9]

The first case of pneumocephalous (cranial aerocele) was reported by Lecat in 1741.[10] In 1884, Chiari diagnosed pneumocephalous in a postmortem examination of a subject with ethmoiditis, and demonstrated a fistulous connection between the ethmoid cavity and the frontal lobe of the brain.[11] In 1913, Luckett[12] provided the first radiographic evidence of intracranial air in a living person.[13]

Pneumocephalous has been described after penetrating head trauma and intracranial surgery, although it has been reported with traumatic nasotracheal intubation, nasogastric tube placement, epidural anesthesia, nitrous oxide anesthesia,[14] meningitis, chronic subdural hematoma and encephalocele.[15] Pneumocephalous has also been reported as a rare complication of a number of otolaryngologic procedures,[16] including functional endoscopic sinus surgery, intranasal ethmoidectomy, nasal septoplasty, turbinate resection, acoustic neuroma resection, infections and congenital anomalies.[17] It should also be noted that CSF leakage associated with pneumocephalous is also not uncommon.

Two mechanisms through which it may occur have been proposed.[18] The first requires the presence of a dural defect, through which CSF leaks until CSF becomes replaced by air, leading to pneumocephalous. A second mechanism is known as the "ball-valve effect." Raised pressure in the middle ear by nose blowing, sneezing, swallowing, coughing, or Valsalva's manoeuver creates a positive pressure gradient, forcing air into the intracranial space. This mechanism attributes a valve-like function to the Eustachian tube. In both mechanisms there must be a connection between the intra- and extracranial space. This can either be a congenital

List of Complications

- Diminished or destroyed hearing
- Vestibular disorders
  - Dizziness, vomiting, unsteadiness
  - fatigue
- Tinnitus
- Headaches and neck aches
  - Occipital neuralgia
- Facial nerve paralysis
  - Difficulty eating, drinking, blinking, smiling
  - Severe droop of half the face
  - Lost or altered sense of taste
  - Dental problems
- Vocal problems due to vocal cord weakness
- Eye problems
  - Dry eye
  - Double vision
- CSF leak (20% risk with translabyringhine and 15% with Retrosigmoid approach).
- Cognitive and emotional difficulties
  - Short-term memory loss
  - Inabilty to concentrate
  - Sense of confusion
  - Language difficulties
  - Drop in IQ
- Hydrocephalus
- Meningitis
- Blood clots, seizures, strokes
- Incomplete tumour removal
- Depression
- Death
- Pneumocephalous

Table 1: List of possible complications for Acoustic Neuroma Surgery

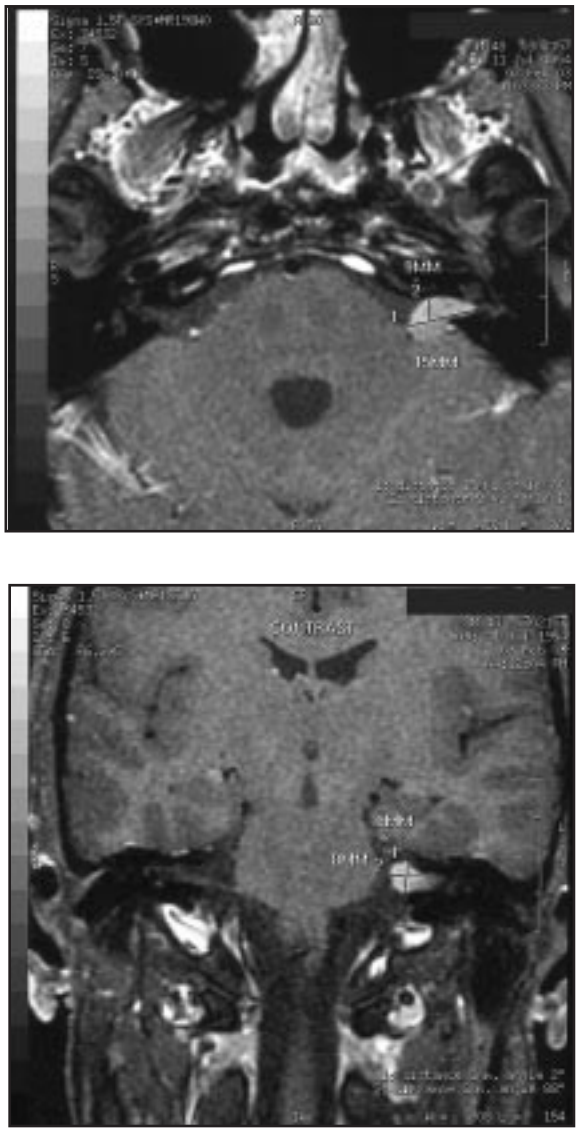

Figure 1a-b: Left acoustic neuroma just medial to the cerebellopontine angle.

bony defect (e.g. in the tegmen tympani), skull erosion that accompanies hyperpneumatization or through surgery.

In other cases reported from this institute[19] it was speculated that air was trapped within the ear canal and the CPA after resection of the tumour when the dura is closed. Since then, the CPA is routinely filled with water prior to closure of the dura. In the case reported here, it was thought that the suction drain placed within the craniotomy flap became partially dislodged at the time the patient increased his intracranial pressure upon sitting up in bed, forcing part of the multi-perforated suction drain to be exposed to the outer environment and henceforth, air being collected into the drain due to positive pressure changes which resulted in collection of air into the frontal lobes.

The presentations of pneumocephalous are often vague and nonspecific.[20] The patient may complain of a headache, nausea, vomiting, lethargy, and an altered state of consciousness and show signs of meningism. The diagnosis is often unsuspected and made only after a computed tomographic scan is obtained. Computed tomography is a highly accurate diagnostic tool and can detect as little as 0.5 mL of air in the intracranial compartment.[21]

In most cases, spontaneous resolution occurs and rarely is further surgery required. However, if surgical re-exploration is indicated, it is best performed via the blind sac subtotal petrosectomy of Fisch.

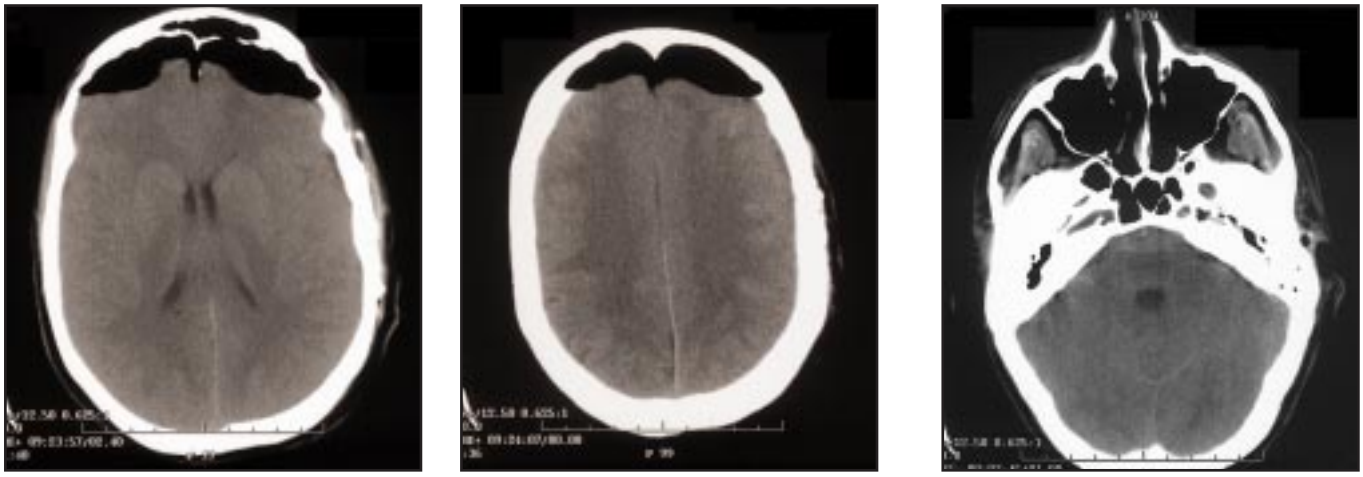

Figure 2a-d: Postoperative pneumocephalous in a 49 year-old male after acoustic neuroma surgery after a surgical drain became dislodged causing loss of conscious and anoxia.

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A randomised clinical trial provides evidence for the long-term effectiveness of physiotherapy in the management of cervicogenic headache

Paul Kelly
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BACKGROUND

A national multicentre randomised trial was undertaken to assess the effectiveness of physiotherapy in the management of cervicogenic headache. This was conducted in five Australian states and in Sydney the trial centre base was the St Vincent's Clinic Physiotherapy Department and involved six therapists.

The research was funded by the NHMRC, Physiotherapy Research Foundation, The University of Queensland Foundation and The St Vincent's Clinic Foundation. This was significant for the St Vincent's Clinic Foundation as it was the first grant given by this body to physiotherapy research. The objective of the trial was to determine the effectiveness of manipulative therapy and a low-load exercise regime when used alone and in combination as compared with a control group. From the physiotherapy clinic Paul Kelly and Neil Munro were involved with assessment and manipulative therapy whilst Carolyn Grinter was involved with collection of data. The study showed that the conservative treatments of manipulative therapy and a specific exercise program are effective for the management of cervicogenic headaches and that the effects are maintained in the long term. The article can be located in "Spine" Vol 27 No.17 2002.

Many thanks to The St Vincent's Clinic Foundation for their contribution. The following is a summary from Professor Jull, physiotherapist.

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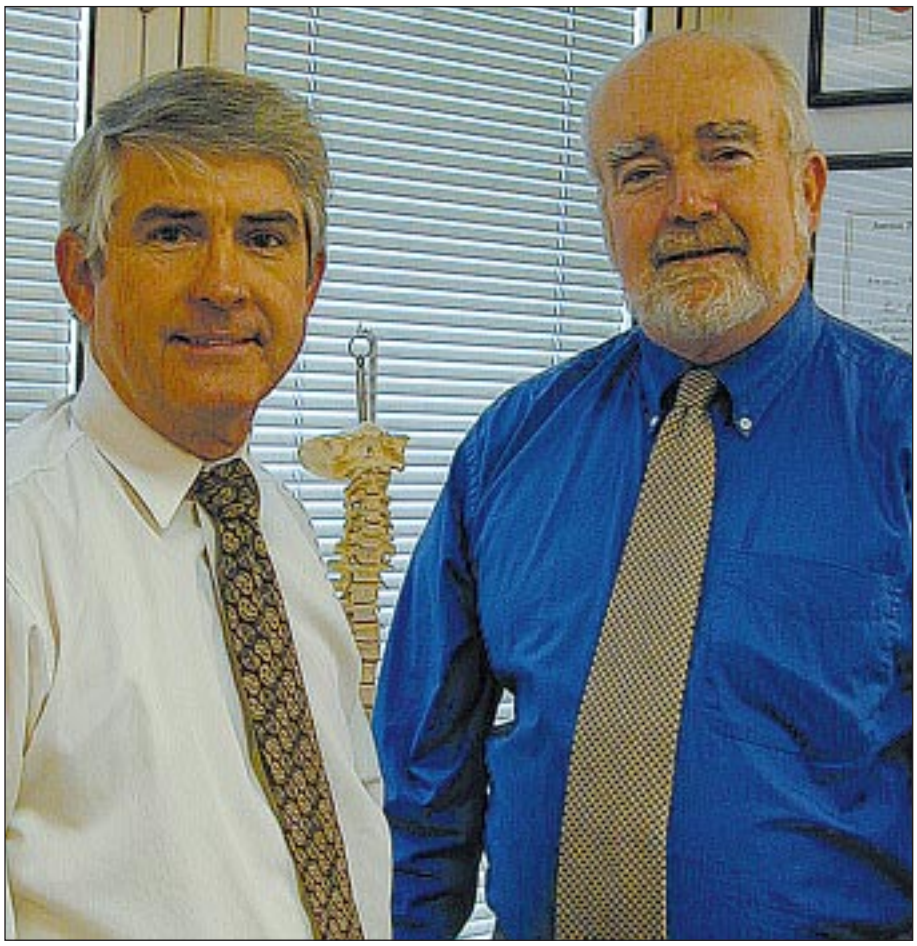

Neil Munro and Paul Kelly

Cervicogenic headache is a term to describe headaches arising from musculoskeletal disorders in the neck. The term represents a potential spectrum of pain sources and pathologies in the upper cervical structures responsible for headache. It is characteristically a unilateral or unilaterally dominant headache without sideshift which is associated with neck pain and commonly provoked by sustained or awkward head and neck postures or movement. Cervicogenic headache is a comparatively common headache type and epidemiological estimates indicate a month prevalence of 2.5 per cent in the general population while that for migranes is 4 per cent. Cervicogenic headache is more prevalent in females but it can affect any age group. There may a history of neck trauma but onset can be insideous and associated with cervical degenerative disease or mechanical overload on the neck from sedentary activities such as prolonged computer use.

The last decade in particular has witnessed a sustained demand on all health care professions to bring together evidence which supports or indeed rejects the effectiveness of their interventions. Conservative treatment such as physiotherapy management is commonly used and recommended for cervicogenic headache but there has been little research into the effects of

such management methods. In consequence, a national multicentre randomised clinical trial was undertaken to assess the effectiveness of physiotherapy interventions.

The clinical trial aimed to assess the effectiveness of two physiotherapy methods for the management of cervicogenic headache. The first was manipulative therapy as a direct treatment of painful cervical joint dysfunction. The second was a new form of low load exercise, which addressed muscle impairment linked with joint pain and dysfunction in cervicogenic headache. The exercise program focussed on the re-education of the deep and postural muscle control of the cervico-brachial region using the principles of segmental stabilization training rather than conventional strength training. The therapies were tested alone and in combination to investigate whether or not there was an additive effect of the combined therapies. Other questions of clinical relevance were also investigated and these included whether there were relationships between changes in frequency of headache characteristics at baseline, which might identify those subjects who responded to treatment.

Methods: The study was a prospective, multi-centre RCT with unblinded treatment and blinded outcome assessment. A randomized permuted block design was used and an independent body implemented the randomization process. Two hundred subjects participated in the study. Subjects, 18 to 60 years of age, were recruited through advertising or referral from general medical practitioners and selected using the criteria for cervicogenic headache described by Sjaastad et al. The active treatment period was 6 weeks. Co-medication from a defined list of analgesics and non steroidal anti-inflamatory drugs was permitted for all groups. Outcome measures for the trial included headache symptomology (frequency, intensity, and duration), a neck apin index, medication intake, patient satisfaction scales and physical tests of the cervical spine. The latter included pain reported on active cervical movements, pain scores on cervical joint palpation, performance in a cranio-cervical flexion muscle test and a photographic measure of the forward head posture position. Measures were taken at baseline, in the week immediately post treatment (week 7) and at three, six and 12 months after the intervention period.

Results and Discussion: The analysis plan focussed on changes in the outcome measures from baseline assessment and analyses were performed on an intention to treat principle. There was only a 3.5 per cent loss to follow-up and the loss was spread across intervention groups. Both manipulative therapy and specific exercise significantly reduced headache frequency, intensity, neck pain and medication intake immediately following treatment compared to the control group. Those differences were still evident at the 12 month follow-up (all $P < 0.05$). Effect sizes were moderate to high and clinically relevant. The treatment effects were very similar for the three treatment arms. A significant additive effect for the combined therapy was not demonstrated, although approximately 10 per cent more subjects who received the combined treatment obtained either complete relief or reached the benchmark of a 50 per cent or better reduction in headache frequency. At the 12 month follow-up, 72per cent of subjects in the active treatment groups reported a 50 per cent or greater reduction in headache frequency, with 42 per cent reporting 80-100 per cent relief at this time. Overall, these results support the clinical effectiveness of the physiotherapy treatments for the majority of subjects.

The interventions resulted in significant reductions in the pain experienced on neck movements and manual palpation of the cervical joints (all $P < 0.05$). Manipultaive therapy provided a better improvement in segmental joint motion than therapeutic exercise but, in contrast, manipulative therapy had no effect on the muscle impairment tested with the cranio-cervical flexion test. The photographic measure of postural form did not change for any inter-vention group across the trial period.

Further analysis indicated that the changes in headache symptoms could not be entirely explained by the changes in the physical impairments and further research is required into he mechanisms of action of the treatments. The presence of dizziness or lightheadedness were the only symptoms which seperated the subjects who did or did not respond to treatment. This indicates that adding specific training for kinesthetic sense may enhance future treatment programs. The age and gender of the subject or chronicity of the headache did not mitigate against a sucessful outcome.

Conclusions: This trial has provided evidence of the long term effectiveness of physiotherapy treatment methods of manipulative therapy and a specific therapeutic exercise regimen for cervicogenic headache. The results indicated that some features of the cervicogenic headache syndrome were improved more with one, the other, or the combined intervention. Therefore the most appropriate recommendation for a rehabilitation program for cervicogenic headache is the use of both manipulative therapy and the specific exercise in combination.

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