PROCEEDINGS

ST VINCENT'S CLINIC, SYDNEY

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QUALITY HEALTH IN AGEING

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PROCEEDINGS

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EDITORIAL

Dr John Roarty

MEDICAL EXECUTIVE OFFICER

ONE of the biggest challenges confronting most of the nationalities of western societies today is the increase in life expectancy. This brings with it increasing demands on budgets allocated for health care to deal with the many diseases and conditions associated with increasing age. It is possible to grow older gracefully and enjoy a healthy lifestyle if we are aware and educated in the manner of prevention of such diseases and in a commonsense way of dealing with the early manifestations of such conditions.

Some of these problems are addressed by several doctors in St. Vincent's Clinic in this issue. Professor Peter Brooks draws attention to the fact that a quarter of the 2.5 million Australians classified as disabled, suffer a muscular skeletal problem, making it the most common cause of chronic disability in this country. Most of these people suffer from soft tissue rheumatism and osteoarthritis. It is interesting to note that there has been such a change in our view of the pathology of osteoarthritis in recent years in that in osteoarthritis the joint represents a real or attempted repair rather than a degeneration or wearing out. Professor Brooks stresses the necessity for education of the community about osteoarthritis and its management, particularly common sense measures such as reduction of weight and the ever important aspect of exercise, particularly to strengthen muscles and maintain joint motion. There are many improvements in the conservative or medical management of arthritis and also in the technique of mini-arthroscopy of some of the small joints (funded by a grant from the Clinic Foundation). However, despite a full trial on all conservative measures some people still are disabled with chronic pain and decreased mobility. Dr Michael Neil describes recent advances in the surgical treatment of arthritis of the knee which will transform the life of the very disabled from the arthritis of the knee to one of freedom of pain and increased mobility.

Dr Paul Kelly describes a very practical approach to the causation, prevention and current management of osteoporosis. Assessment of bone density is now possible and where such evidence indicates a potential for osteoporosis, correct management can be instituted with particular reference to diet, including calcium and vitamin D intake, the administration of hormone replacement and its relationship to cortico steroids. Dr Kelly also emphasises the importance of exercise in this regard.

Recent advances in the management of arterial disease are outlined by Professor Tracy and the new concept of the co-operation between vascular physician, the vascular laboratory and vascular surgeon is emphasised. Recent techniques with balloon angioplasty to overcome vascular occlusion have given patients with arterial disease much comfort and prevented major arterial surgery. However, in certain severe obstructions, safe vascular surgery can now be undertaken to improve circulation of limbs in jeopardy.

Parkinsons Disease, and the disabling and at times uncontrollable tremor associated with it, has been a challenge to scientists over many years. Drs O'Sullivan and Pell give new hope to sufferers of this disease, allowing patients to control the degree of their tremor. This ingenious method is carried out by an electrode which is placed into the thalamus and connected to a pacemaker beneath the skin and regulated by a computer which can programme stimulation of the device. Although their experience is early at this stage, they expect to have similar results to Professor Benabid of France who has performed the procedure in 130 patients, all of whom have had relief of the tremor.

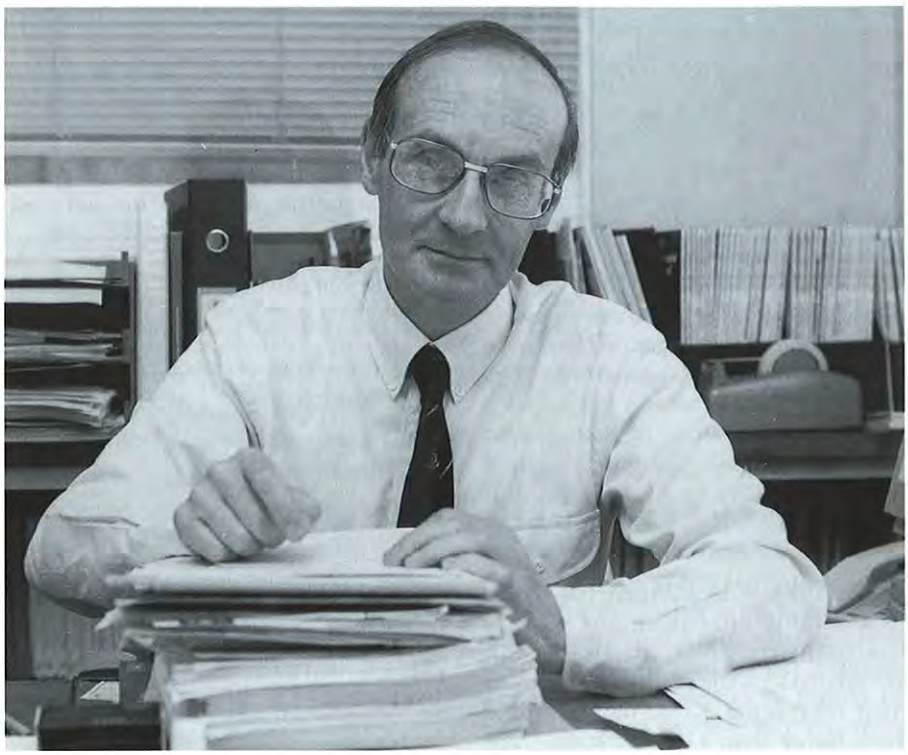
The prevalence of asthma in Australia is outlined in Dr Janet Rimmer's article and in a very comprehensive and detailed manner she has described current concepts on its causation and the management.

The St. Vincent's Clinic Foundation awarded grants for 11 projects in 1993. These grants have assisted in the development of new studies and investigations. Professor Michael O'Rouke and his team described the assistance they have received in the development of a new simple, reliable measurement of the arterial pulse, particularly in the variation of blood pressure in daily activities, sitting, standing, lying, eating, exercise, and the effects of vasodilator drugs. The results of other projects from the Foundation will be reported as they are completed.

A brief summary of the research programs which the St. Vincent's Clinic Foundation supported is included in this issue.

Professor Peter Brooks

Osteoarthritis in the 90s



EPIDEMIOLOGY

Nearly a quarter of the 2.5 million Australians classified as disabled suffer a musculoskeletal problem, making it the most common cause of chronic disability in this country. Most of these people suffer from soft tissue rheumatism and osteoarthritis (OA), problems which will increase dramatically over the next two decades with our ageing population.

A postal survey of over 25,000 residents in the United Kingdom estimated the prevalence of disability associated with rheumatic disorders to be 82 per 1000 population aged at least 16 years. Arthritis (primarily osteoarthritis) was the most common cause of disability (47 per 1000) followed by back and neck disorders (25 per 1000), soft tissue disorders (18 per 1000) and rheumatoid arthritis (4 per 1000). Similar surveys in Canada have suggested a comparable degree of community disability, osteoarthritis and soft tissue rheumatism being the most common causes. The majority of research funds still seem to be spent on the inflammatory forms of arthritis rather than degenerative forms and yet joint replacement, for example, is becoming the most commonly performed operation in this country and Quan et al have already estimated a total cost of knee replacements in the United States to be in excess of $US2.3 billion annually.

Low back pain continues to be a major cause of sickness and invalidity benefits with a dramatic increase over the last decade (Waddell, 1993) Figure 1. Management of back pain has changed significantly over the past few years with increasing emphasis on early mobilisation rather than rest with few patients requiring bed rest for more than one to two days unless there is severe nerve root pain. Rest and restriction of activities are absolutely contraindicated for chronic back pain. The biopsychosocial model, in which the pain and (often minor) injuries are subsequently influenced by the patient's pre-existing attitudes and beliefs, by psychological stress, by the development

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Professor of Medicine,
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of illness behaviour and by the social environment, is emphasised by Waddell who points out that there needs to be a significant change in the behaviour of doctors in their approach to back pain.

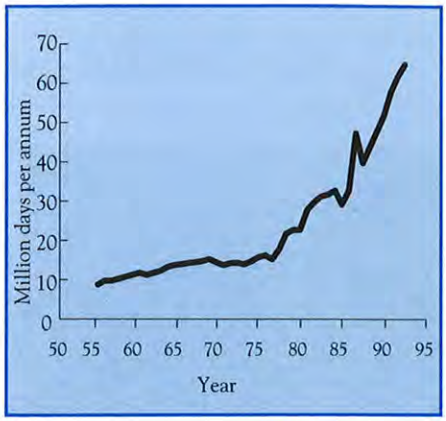


Figure 1. Increase in payment of sickness and invalidity benefit for back pain in the United Kingdom. Unpublished data supplied by the Department of Social Security.

Aetiopathogenesis of Osteoarthritis

Over the last decade there has been a considerable change in our view of osteoarthritis in that it is now appreciated that the pathology of an OA joint represents a real or attempted repair rather than a degeneration. The concept that OA can largely be explained as a natural reaction of synovial joints to injury and is a product of normal remodelling or repair processes in joints is now accepted. Synovial inflammation may also play a role although it is probably secondary and deposition of calcium containing crystals in the cartilage and in the synovium may also lead to joint damage. Cartilage is made up of a dense matrix of collagen and proteoglycans with a large amount of water. It is now clear that cartilage is a dynamic tissue and that cytokines produced in the joint (primarily from the synovium) can influence chondrocyte function. Metalloproteinase enzymes can break down cartilage, collagen and proteoglycan, again leading to joint destruction. These are present in osteoarthritic synovial fluid and are released from connective tissue cells in an inactive form which can be activated by proteolytic removal of a short peptide. Naturally occurring tissue inhibitors of metalloproteinases (TIMP) will bind tightly to the activated enzyme and interfere with its activity. These natural inhibitors of cartilage breakdown may be deficient in OA. Biomechanics also make a major contribution to our understanding of OA. The synovial joint is a mechanical organ and the importance of physical forces, such as those produced by abnormalities of joint shape or by stress applied to joints, have been recognised for a number of years. The various factors thought to be important in producing osteoarthritis are shown in Figure 2. Dieppe and Kirwin 1994).

Clinical

It is now clear that osteoarthritis is not one disease. Subsets of osteoarthritis need to be defined depending on -

1. The joint involved
2. The number of joints involved
3. The presence of associated crystal deposition
4. The presence of marked clinical inflammation
5. The radiographic bone response (atrophic or hypertrophic)

For example, one of the best recognised subsets is that of nodal generalised osteoarthritis which is characterised by -

1. Polyarticular interphalangeal involvement of fingers
2. Heberden's and Bouchard nodes
3. Female preponderance
4. Peak onset in middle age
5. Good functional outcome
6. Predisposition to osteoarthritis of the hip, knee and spine
7. Marked familial predisposition

Large joint osteoarthritis, such as that affecting the hip and knee, are common in the ageing population but have different prognoses depending on which part of the joint is involved. What is clear from long term studies is that not all patients with osteoarthritis progress and some, in fact, can have resolution of both symptoms and radiological changes.

Investigations

Osteoarthritis is a clinical diagnosis which is often confirmed by radiology. One must remember that there is a poor correlation between clinical and radiological features. Plain radiology facilitates subgrouping of osteoarthritis by demonstrating the distribution of OA changes, emphasising hypertrophic or atrophic appearances and demonstrating additional features such as calcification of the cartilage or other structures. Microfocal radiology is a magnification

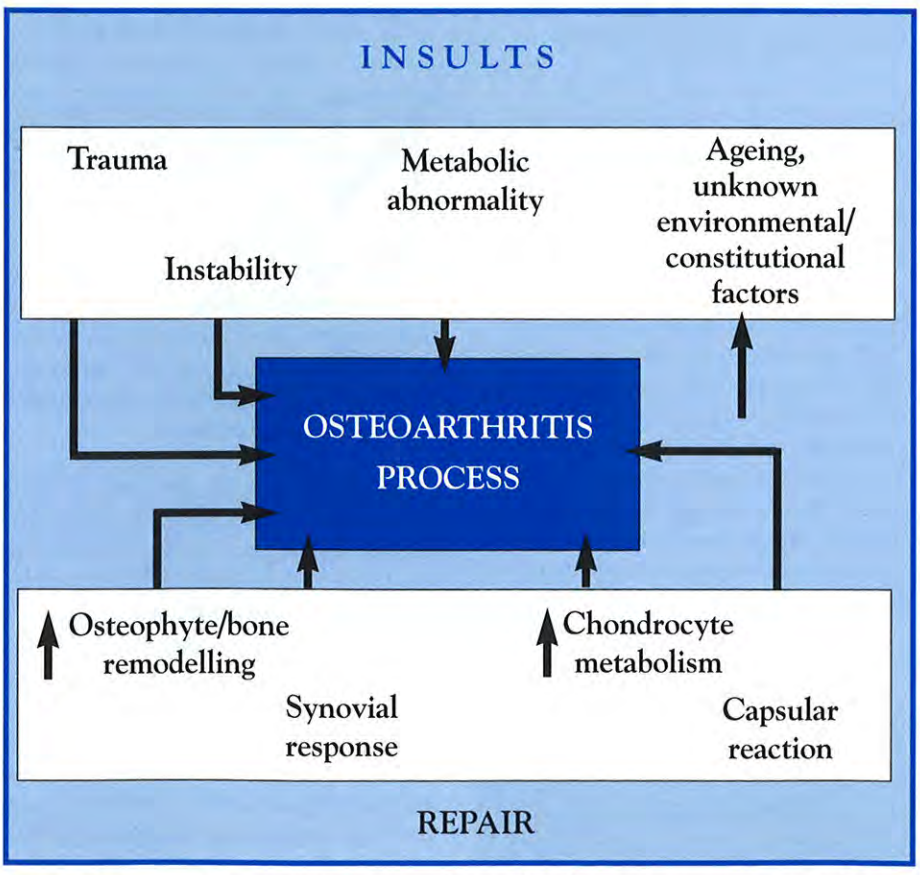


Figure 2. Diagrammatic representation of osteoarthritis as the inherent repair process of synovial joints

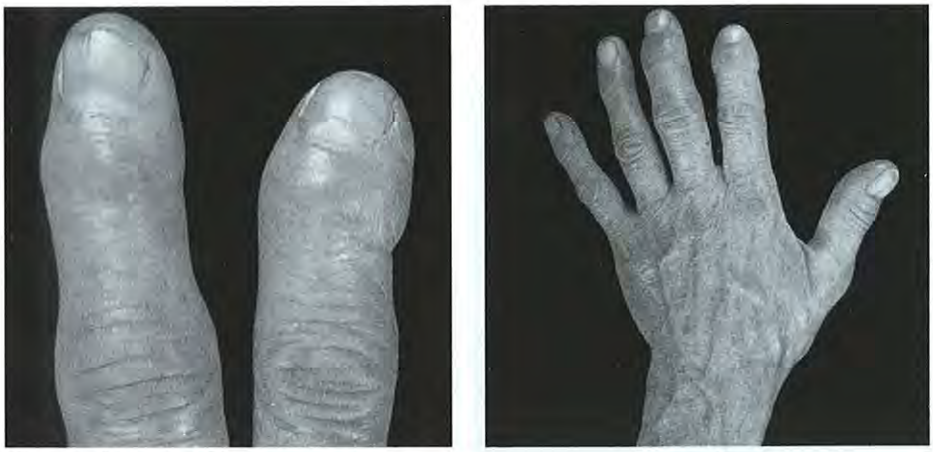


Figure 3. Heberden's Nodes.

technique which allows higher resolution imaging but is not useful for routine work. Ultrasonography can permit imaging of cartilage and tendons and may prove of value in the early detection of cartilage abnormalities. MRI may also be helpful but more work needs to be done. For example a recent review of MRI in pain free individuals showed lumbar disc abnormalities in 50% of persons with no history of back pain. (Jensen et. al 1994). Radionucleide scans may also be useful, particularly as there is evidence that a "hot" scan may be a predictor of rapid progression of OA. As it is now clear that cartilage is a dynamic substance, a variety of markers of cartilage breakdown are now being detected in synovial fluid, serum and urine. Cartilage breakdown products such as proteoglycan, keratan sulphate and the C-terminal propeptide of type II collagen have been demonstrated in synovial fluid and in blood. Breakdown products of collagen cross links derived from cartilage and bone have also been shown in urine. These markers may be extremely useful in monitoring progression of osteoarthritis and response to treatment. (Wollheim 1994).

Management of Osteoarthritis

A general approach to the management of symptomatic osteoarthritis is outlined as follows:

1. Education about osteoarthritis
2. Protect compromised joints from excessive loading -
   - Reduce obesity
   - Modify inappropriate daily/occupational activities
   - Use a walking stick
   - Shock absorbing innersoles
   - Correct leg length discrepancy.
3. Maintain joint motion and stability
   - Regular movement, little and often
   - Muscle strengthening exercises
4. Reduce pain and stiffness -
   - Physiotherapy
   - Intermittent analgesics
   - Consider occasional courses of non-steroidal anti-inflammatory drugs
   - Consider peri- and intra-articular injection
   - Consider transcutaneous electrical nerve stimulation and nerve blocks for severe pain.
5. Reduce impact of pain and disability -
   - Treat depression, anxiety
   - Consider coping strategies
   - Modify patient environment to reduce handicap
6. Consider surgery for persistent and severe pain and/or disability

Simple education techniques have been shown to be helpful in reducing pain and disability in osteoarthritis.

It is has now been appreciated that NSAIDs are not the routine treatment for OA because of their potential for side effects. A number of recent two year placebo controlled trials of NSAID therapy of osteoarthritis of the knee provide interesting insights. In these studies, comparing placebo (paracetamol) with slow release voltaren or naprosyn, (Dieppe, 1993, Williams et. al. 1993) a significant number of patients were able to complete two years of treatment on a paracetamol alone. From these data it would seem that up to one-third of patients with OA of the knee previously maintained on NSAID therapy can be adequately maintained on analgesics alone. These studies also provide evidence for the safety of long term paracetamol in doses up to 2 g daily.

Over the next decade an exciting array of compounds will be trialed in patients with osteoarthritis directed not at relieving pain but at modifying cartilage breakdown (Creamer and Dieppe, 1993). These include glycosaminoglycan derivatives such as pentosan polysulphate (Cartrophen), oestrogens, interleukin-1 and tumour necrosis factor inhibitors, hyaluronic acid and inhibitors of collagenase. The challenge will be to establish long term, properly controlled trials in patients with osteoarthritis which use firm endpoints of cartilage integrity and function (Thieler et al 1994). To this end, such techniques as miniarthroscopy and chondroscopy (a technique of viewing the surface of the articular cartilage and possibly directly measuring some of the functional characteristics - tensile strength and water content) are being developed. The technique of miniarthroscopy of synovial joints is being developed at the Clinic by the rheumatology and orthopaedic groups (funded by a grant from the Clinic Foundation). This is an exciting new outpatient technique which allows direct visualisation of the cartilage surface and the ability to biopsy the synovial lining under direct vision and on multiple occasions. Already this technique is being applied to the management of inflammatory forms of arthritis such as rheumatoid arthritis and plans to use the technique in osteoarthritis trials are progressing.

The identification of clear risk factors for osteoarthritis of the knee such as obesity, previous knee injury and frequent knee bending as described by Felson from the Framingham Osteoarthritis Survey (1990), has for the first time identified a group of patients who will progress to osteoarthritis. Development of drugs which might actually slow or reverse the process is

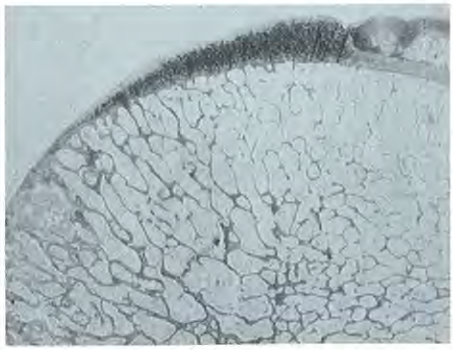


Figure 4. Section of bone showing cartilage loss and bone overgrowth (osteophyte formation)

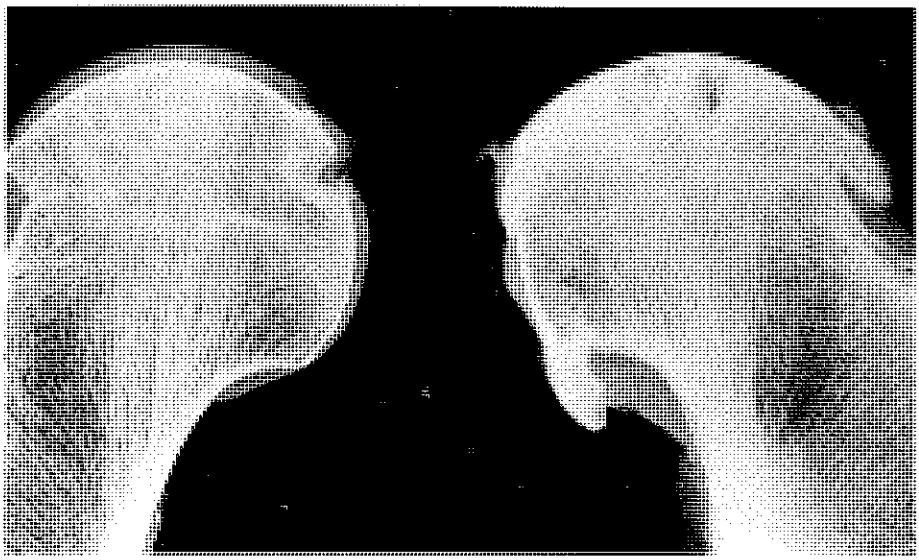


Figure 5. X-ray of hip showing normal cartilage (L) and loss of cartilage and osteophyte formation (R)

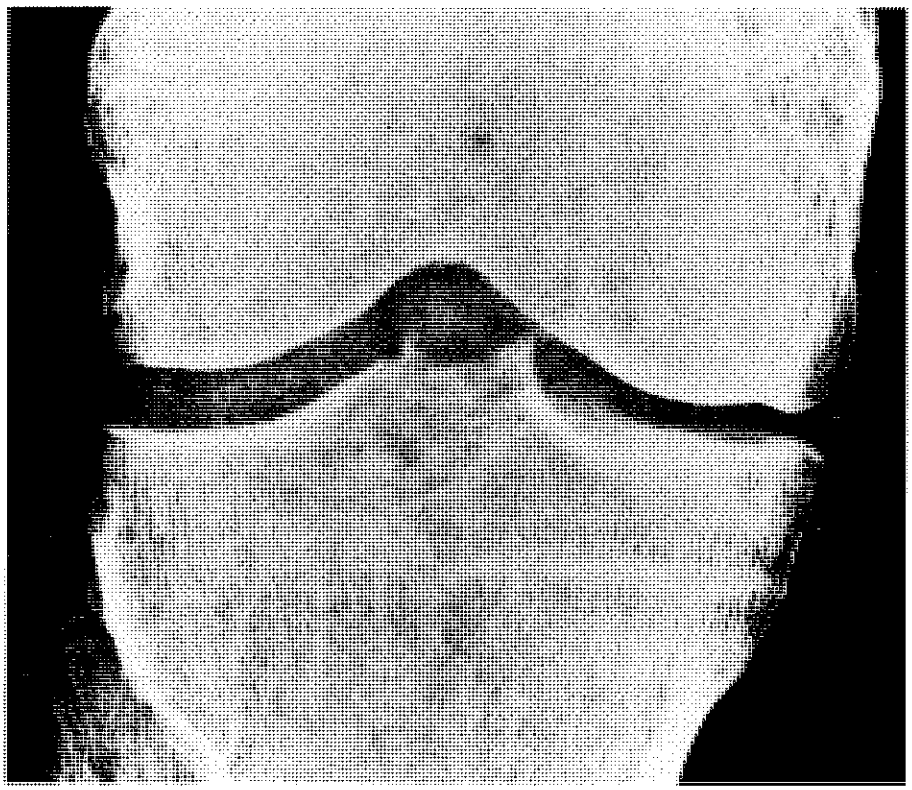


Figure 6. X-ray of knee joint showing cartilage loss and osteophyte formation with boney sclerosis

exciting in that these drugs can now be tested on this type of population in a properly controlled fashion. The trials will need to be carried out over a significant period of time but, if successful, will be enormously beneficial to our ageing population and reduce the morbidity due to pain.

Surgery with joint replacement will remain as an extremely useful treatment for those patients with severe disabilities. New developments in fixation (cementless) and the use of new biomaterials will continue to improve function after joint replacement and reduce the chance of loosening.

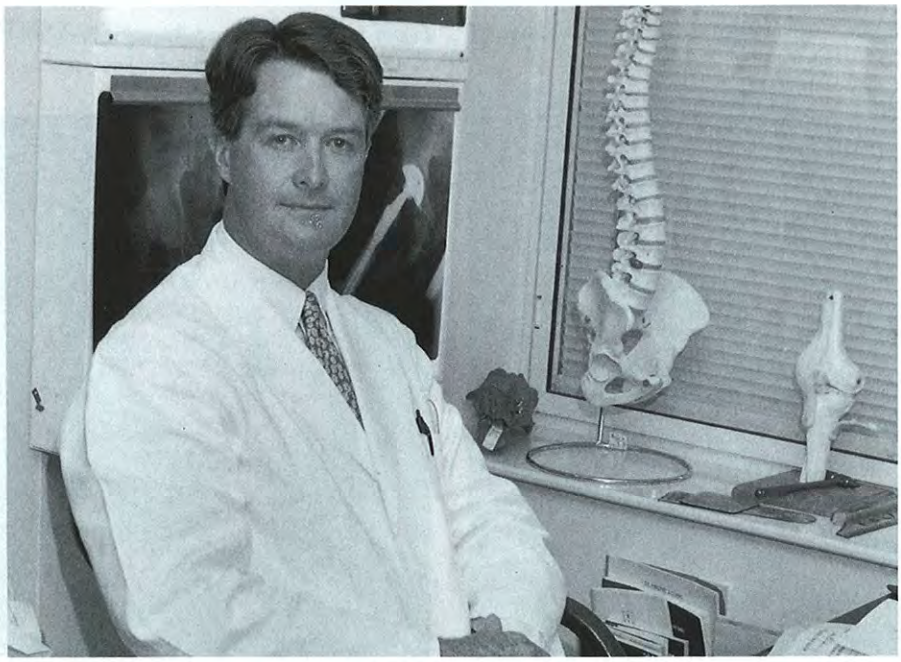
Osteoarthritis remains a fascinating enigma - is the problem in the cartilage, in the synovium or in the bone? Like many things in medicine, it is probably in all three, to varying degrees. Recent advances in our understanding of the basic biology of cartilage, in the development of new strategies and drugs for the treatment of osteoarthritis and an emphasis on controlling pain and improving function mean that that all patients with osteoarthritis can now be helped to some degree.

References

1. Quan JP, Michet OJ, Wilson MG, et al. Total knee arthroplasty. A population based study. Mayo Clin Proceedings, 1991; 66: 589-595.
2. Waddell G. Simple low back pain: rest or active exercise? Ann Rheum Dis, 1993; 52: 317-319.
3. Wollheim, F. New insights into joint damage from analysis of released biochemical markers. Brit J. Rheumatol. 1994: 33;1-4.
4. Dieppe P, and Kirwan J. The localisation of osteoarthritis. Brit J. Rheumatol, 1994:33;201-204.
5. Dieppe, P., Cushnagen, J., Jasani, M.K., McCrea, F., and Watt, I. A two year placebo-controlled trial of non-steroidal anti-inflammatory therapy in osteoarthritis of the knee joint. Brit J. Rheumatol, 1993:32;595-600.
6. Williams, H.J., Ward, J.R., Egger, M.J. et. al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. Arthritis Rheum 1993; 36:1196-1206.
7. Creamer, P. and Dieppe P.A. Novel drug treatment strategies for osteoarthritis. Brit J. Rheumatol, 1993:20; 1416-1464.
8. Felson, D. The epidemiology of osteoarthritis: results of the Framingham Osteoarthritis study. Semin. Arthritis Rheum: Semin. Arthritis Rheum 1990 (Supple) 42-50.
9. Thieler, R. Ghosh, P., and Brooks P. Clinical biochemical and imaging methods of assessing osteoarthritis and clinical trials with agents claiming 'chrondromodulating activity'. Osteoarthritis and Cart 1994:2;1-23.
10. Jensen, M.C., Brant-Zawadzki, M.N., Obuchowski, N. et. al. Magnetic resonance imaging of the lumbar spine in people without back pain.

Dr Michael Neil

Surgical treatment of Osteoarthritis of the Knee



Introduction

Osteoarthritis (OA) is a common, crippling disease with the hip and knee joints being frequently affected. Epidemiological studies estimate the incidence of OA to be approximately 50% in males and females by the age of 55, the incidence increasing dramatically to 85% by the seventh decade.

It is clear that OA has the highest morbidity of all diseases affecting mankind and as the longevity of patients in Western society increases, the problems associated with the management of this disorder become more acute.

Whilst there are new and exciting medical therapies developing in the treatment of OA of the knee, surgical treatment has a great deal to offer with increasingly better outcomes and less morbidity. Surgical options in the treatment of OA of the knee are described in Table 1.

Surgical Options in Treatment of OA knee

1. Debridement	- Open (Pridie) - Arthroscopic
2. Osteotomy	- Upper tibial - Lower femoral
3. Joint replacement	- Unicompartmental -Total

Table 1.

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Orthopaedic Surgeon
St Vincent's Clinic

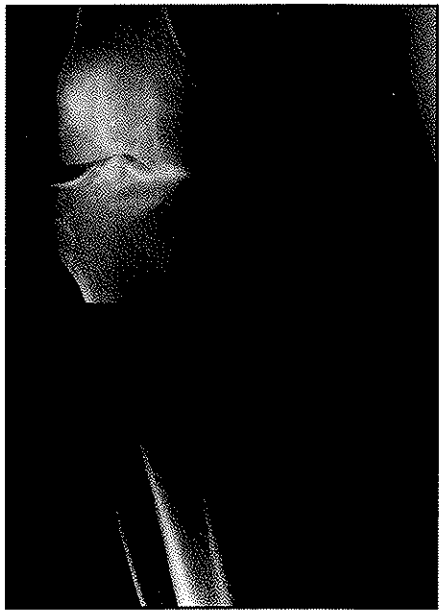

Figure 1.(a) Medial compartment OA knee with varus (bowing) deformity

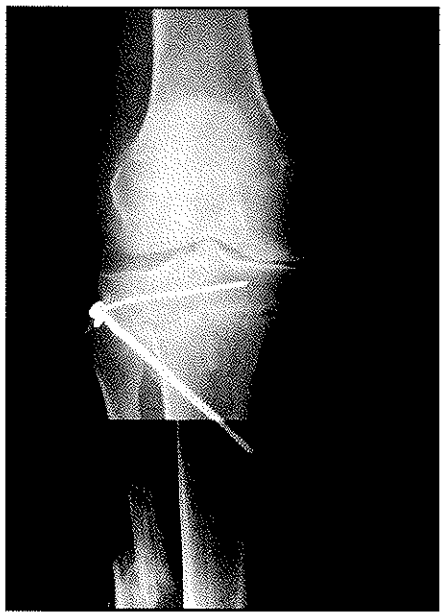

Figure 1.(b) Correction following upper tibial osteotomy. Note return of medial joint space

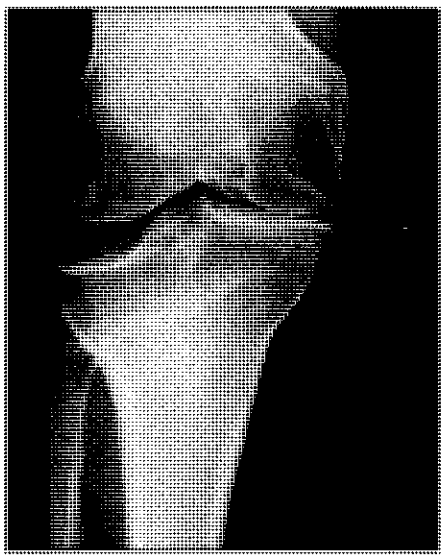

Figure 2.(a) OA knee joint with previous upper tibial osteotomy

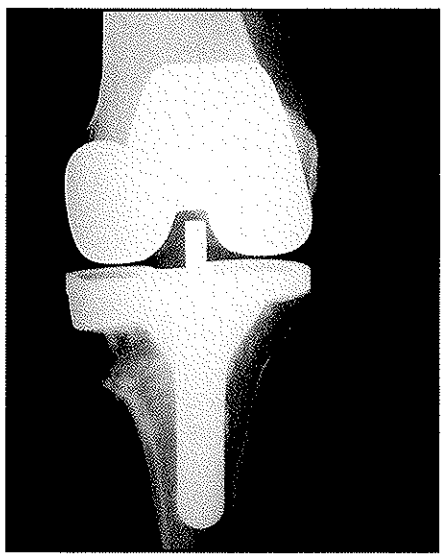

Figure 2.(b) Post-operative total knee replacement with modular wedge laterally

1. DEBRIDEMENT: Open debridement (Pridie procedure) was frequently used prior to the advent of joint replacement to improve the comfort of osteoarthritic knee joints. However, it has significant morbidity and has now been superseded largely by total joint replacement. However, arthroscopic debridement is commonly carried out for patients whose symptoms are either acute or not severely disabling to warrant more major surgery. The advantage of arthroscopic debridement is that it may significantly improve the pain in the osteoarthritic knee joint and involves a day only procedure with minimal morbidity. Arthroscopic debridement allows for complete visualisation of the knee with removal of torn menisci, loose bodies, shaving of unstable articular cartilage (chondroplasty) and drilling of bare bone defects to encourage fibro cartilaginous ingrowth (osteoplasty). The joint is thoroughly irrigated and lavaged and part of the success of this procedure may be in the washing out of proteolytic enzymes which facilitate cartilage break down.

Arthroscopic debridement can be repeated when necessary. However, the result of this technique may be short lived and in some patients is unpredictable.

2. OSTEOTOMY: Osteotomy (which literally means "cutting the bone") may be carried out either in the upper tibia or lower femur and was first introduced in 1958 in the treatment of osteoarthritis of the knee. The principle of this operation is to realign a knee joint with significant deformity and primarily unicompartmental disease. The operation aims to transfer load from a diseased compartment of the knee joint to a relatively normal compartment (see Figures 1a and 1b). The success of this procedure depends on accurate pre-operative planning to determine the desired degree of mechanical correction to be achieved and to be able to carry this out intra-operatively. The osteotomy is usually internally fixed with a metallic fixation device to allow early range of motion and weight bearing.

This operation is usually offered for patients who are too young or too active to undergo joint replacement surgery, and to "buy time" before total knee replacement is required. The draw back of this operation however, is that the success rate is only 85% in terms of pain relief and approximately 50% of these patients will require further surgery, usually conversion to a total joint replacement within 5 to 10 years. Crutches are usually required for a least 6 weeks until the osteotomy has united followed by at least 3 months rehabilitation.

3. JOINT REPLACEMENT:

Total knee replacement has become the standard surgical care for patients with advanced symptomatic osteoarthritis of the knee in whom all conservative treatments have failed. In the early 1970s the implants used to replace the diseased knee joint were fairly primitive, non-anatomical and came with poor instrumentation. However, over the past 10 years the prostheses which have been developed are extremely sophisticated and aim to reproduce the anatomy and kinematics of the normal human knee joint. Added to this, it has become clear that alignment and accuracy of implantation of a knee replacement are critical to the longevity of the implant. The instrumentation designed to implant knee prostheses has also become extremely accurate with high reproducibility of anatomical alignment following surgery.

The indication for knee replacement surgery is usually in a patient who has significant and disabling pain, particularly night pain, and who does not wish to run. Gross deformities can be corrected with appropriate implantation of total knee prostheses (see Figures 2a and 2b). Also in patients with severe bilateral disease it is becoming increasingly common to carry

out bilateral simultaneous total knee replacements under the one anaesthetic (see Figures 3a and 3b). This does not appear to increase the mortality or morbidity rate and decreases the overall rehabilitation time and costs.

The failure rate for a total knee replacement in terms of loosening requiring revision depends on the age and activity of the patient, but an overall figure of 2% per year is well accepted. This would imply that a patient who is aged 60 at the time of knee replacement has a 40% chance that the implant would have failed and required revision by the age of 80. Revision surgery is not as successful as primary replacement and therefore joint replacement surgery is usually offered for those patients in whom it is thought that there is a high likelihood that the implant will last them for life. In the younger more active patient debridement or osteotomy is preferred.**Unicompartmental knee** replacement (see Figures 4a and 4b), while developed at the same time as total knee replacement, has not gained widespread acceptance by the orthopaedic community. However, there are increasing reports that unicompartmental replacement yields a higher initial success rate and fewer early complications than does upper tibial osteotomy. Compared with total knee replacement, it allows preservation of both cruciate ligaments as well as bone stock in the opposite and patello femoral compartments. Moreover, in several publishing large studies, unicompartmental replacement has an equivalent pain relief and early rehabilitation and similar long term functional results compared with total knee replacement counterparts. In fact in Sweden, where there is a comprehensive followup of all joint replacement carried out nationally, over 50% of knee replacements are unicompartmental.

The advantage of unicompartmental replacement in the patient with primarily medial or lateral compartment disease, is that the initial success rate in terms of pain relief is far higher than for upper tibial osteotomy and functionally the patient is usually better than a total knee replacement. The patient often reports that the knee feels more like a normal knee than a prosthetic knee due to retention of most proprioceptive fibres.

If the unicompartmental knee replacement fails then revision should be easier than revision of a failed total knee replacement.

Summary

Surgical treatment of osteoarthritis of the knee has improved significantly over the last decade with the advent of arthroscopic debridement and with improved design and longevity of prosthetic implants. During recent years there has been an increase in good to excellent results of total knee replacement with revision rates declining, due to improved technical expertise and sophistication of both implant design and instrumentation. Whilst the scientific and medical community push with increasing vigour for a "cure" for OA, or at least a cartilage preserving drug, surgical treatment offers a very predictable high quality outcome in a large number of patients suffering with this debilitating disease.

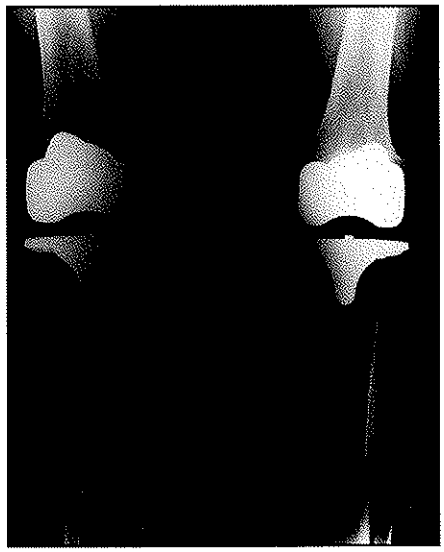

Figure 3.(b) Post Bilateral simultaneous total knee replacement

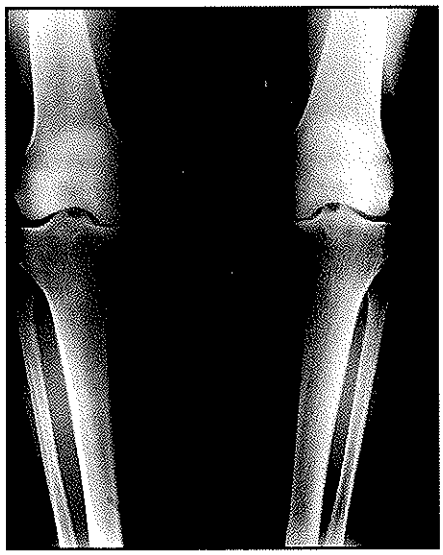

Figure 4.(a) Pre-operative medial compartment OA knees

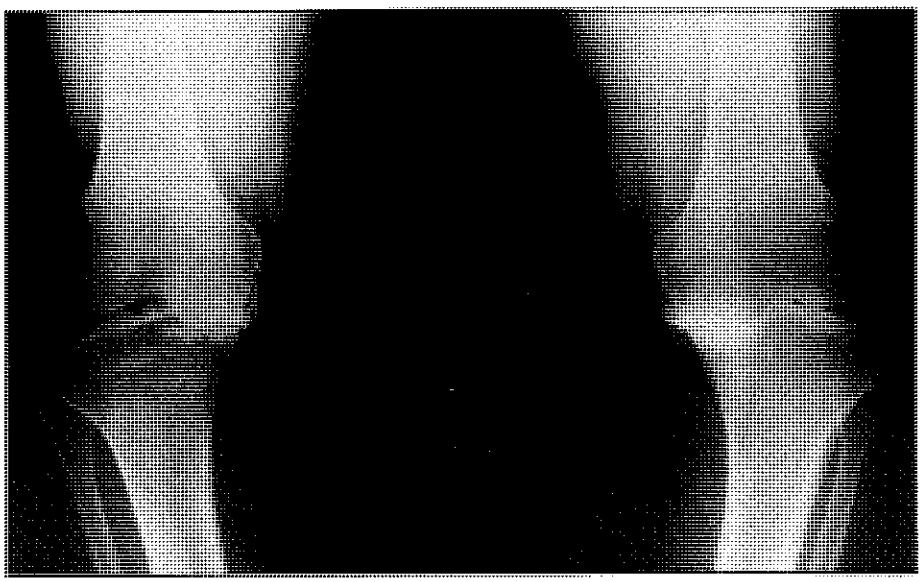

Figure 3(a) Bilateral OA knees

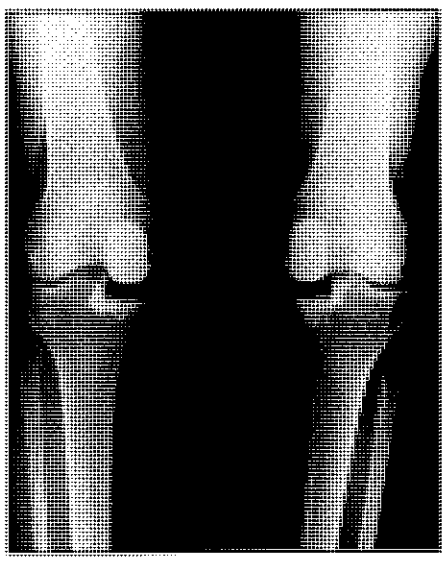

Figure 4.(b) Post-operative bilateral medial unicompartmental replacement

Professor Michael F O'Rourke

Reflections on the Arterial Pulse

The arterial pulse is the oldest physical sign in medicine. Physicians of old were often portrayed looking at the patient, with their fingers over the radial pulse at the wrist. Examination of the pulse combines a clinical skill with an even older healing rite - the touching of flesh, the laying on of hands. The skilful physician combines both the art with the science of medicine in holding the patient's arm at the wrist and palpating the arterial pulse.

In the Western world, the most venerated written works on the pulse were those of Galen, whose teachings in the second century AD went unchallenged for well over 1,000 years. In the early 19th Century, the work of Bright from London on kidney disease, high blood pressure, stroke and heart failure, stimulated a search for better methods of measuring stresses on the heart and arteries; this led to development of the sphygmogram (which measures the arterial pulse), then of the cuff sphygmomanometer (which measures the highest and lowest limits of the brachial pressure wave). The sphygmogram was widely used in clinical practice 100 years ago, and was used to identify hypertensive subjects, and to study the effects of drugs. The first description of nitroglycerine as treatment for angina pectoris in 1879 (Figure 1) displayed sphygmographic traces showing the effects of this drug on the radial pulse. The technique of sphygmography however was abandoned when the electrocardiogram was introduced and the sphygmomanometer popularized in the early part of the 20th Century. Such clinical application led to simplistic notions on blood pressure, including the idea that systolic pressure is a manifestation of cardiac strength (so that high values are innocuous) and that diastolic pressure is a manifestation of arteriolar tone (and so is the principal manifestation of hypertensive disease). All of these notions are currently under review in consequence of recent large scale trials which show that systolic pressure is more important than diastolic in predicting mortality and morbidity from cardiovascular events. These trials question the old entrenched views which have come from uncritical acceptance of numbers obtained with the cuff sphygmomanometer.

In recent years there have been enormous advances in technology. The arterial pulse can now be recorded more

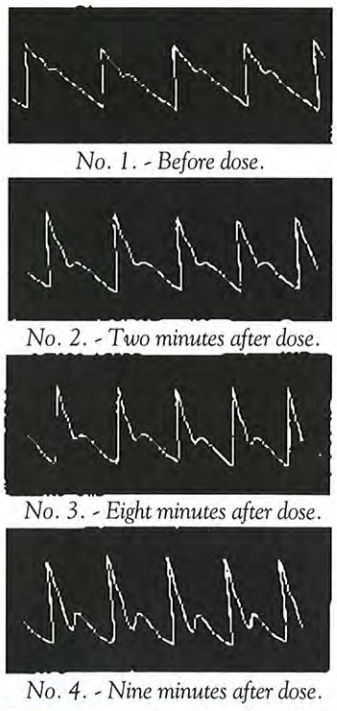

Figure 1 Sphygmograms published by W Murrell in 1879, showing the effects of nitroglycerine on the radial artery pulse. This was the first article to describe the benefit of nitroglycerine in treatment of angina pectoris. Nitroglycerine remains the mainstay in treatment of angina pectoris. Our studies can now explain the changes in wave form after nitroglycerine as corresponding to a substantial decrease in pressure during systole (cardiac contraction) in the left ventricle of the heart and its major outlet (the ascending aorta) and so explain the drug's beneficial action. (From: Murrell W. Nitroglycerine as a remedy for angina pectoris. Lancet 1879;1:80-81, 151-152,225-227).

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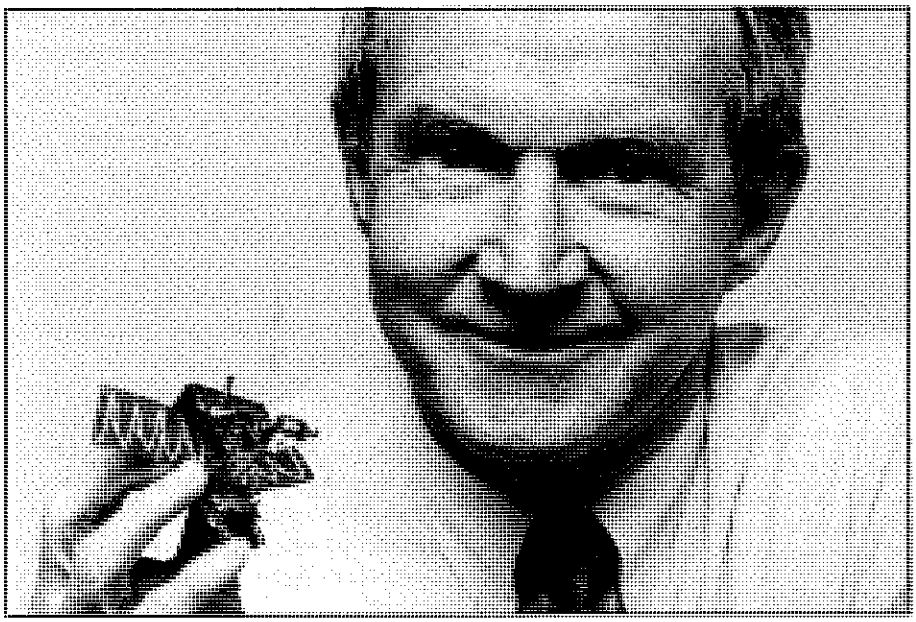
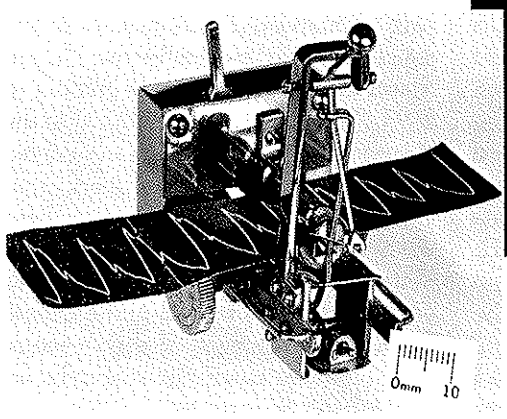


accurately than ever before. Additionally, the mechanisms responsible for pulse contour are now understood, and with the aid of modern digital computers, the pulse can be analysed in the same way that pulsatile phenomena are treated by mechanical, electrical, acoustic or aeronautical engineers. These advances however have not been applied widely to clinical problems, and the study of the arterial pulse by clinicians plays an even lesser role now than it did in the late 19th Century. This is an enigma. The modern physician certainly is well versed in developments in biochemistry and in genetics, and it is surprising that he should overlook similar advances in physics, and developments which his contemporaries in hydraulic and electrical engineering utilize daily in their professional lives.

Our group has chosen to tackle this forsaken area. We have made considerable headway, and see much new understanding and great clinical benefit to come from further research. The basis of our work was the foundation laid by fundamental studies conducted by an Australian physiologist, Michael Taylor, with two British scientists in London during the 1950s. These studies established valid engineering and mathematical approaches that could be applied to the study of the pulse and pulsatile phenomena in arteries. These approaches are now so much easier to apply through use of the powerful computers that were not available in the 1950s, but which are now readily available and widely used, though often used just as word processors. The major finding of Taylor's work was that the arterial pulse undergoes strong reflection so that many of the most prominent features of the arterial pulse are due to wave reflection, or echoes, superimposed on the initial pulse generated by contraction of the heart itself.

Our goal ten years back was to obtain a robust, reliable, and accurate method for measuring the arterial pulse non-invasively:- i.e. a modern day version of the 19th century sphygmogram. We developed such an instrument in association with Huntly Millar of the Millar Instrument Company of Houston, and documented its vast superiority over previously available sphygmograms (Figure 2). We used this instrument to show differences in the arterial pulse at different sites in the body, and the effects of aging, and of drugs. In his doctoral thesis and subsequent publications, Ray Kelly established normal age-related pulse wave patrerns in a study of over 1000 normal subjects and investigated effects of disease states and drugs on the pulse contour. With respect to drug therapy, our most important finding was that vasodilator drugs such as nitroglycerine have a far greater effect in lowering systolic blood pressure at the heart and in central arteries than at the brachial artery where pressure is recorded conventionally (Figure 3). Hence we showed that conventional monitoring could systematically, and markedly, underestimate the beneficial effects of these drugs. Such findings have now been validated by others. The differential effect on systolic pressure in central and peripheral arteries can be explained on the basis of difference in timing of wave reflection. With respect to aging change, we were able to show that increase in systolic pressure over a life span in man is greater at the heart and in central arteries than at the brachial artery where pressure is conventionally recorded, and that such a boost to systolic pressure is largely due to early and exaggerated wave reflection. Two academic visitors on Sabbatical leave (Professor Toshio Yaginuma, Omiya, Japan and Professor Wilmer Nichols, Florida, USA) contributed substantially to this work, and have extended it with their younger collaborators in their own countries. The benefits that have flowed from these associations provide an example of the value in having sabbatical leave visitors at one's own institution.



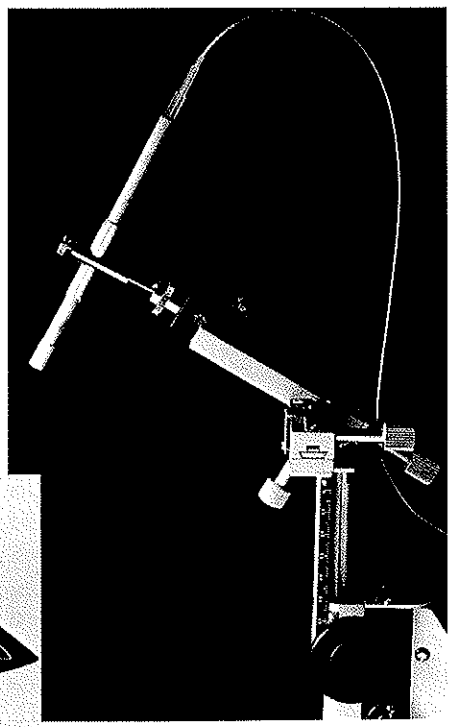


Figure 2. The mechanical Dudgeon sphygmogram as used by Sir James Mackenzie around 1900 (inset), and the high-fidelity electronic tonometer developed with Huntly Millar in 1985

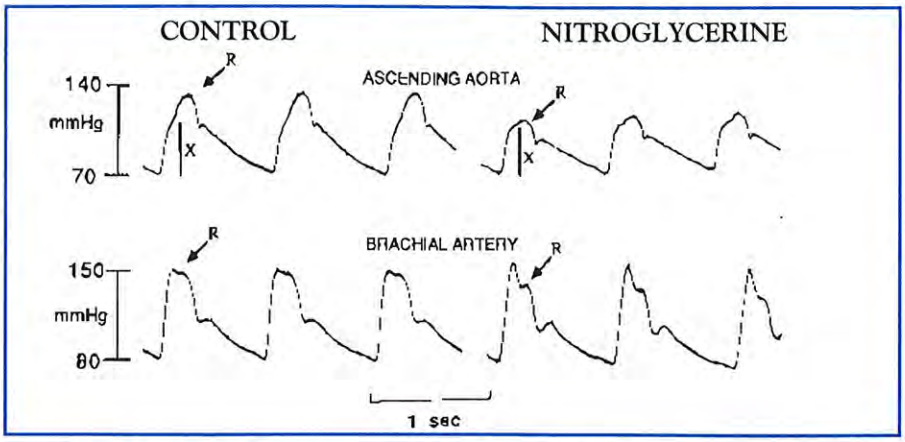


Figure 3. (a) Recordings of ascending aortic pressure (above) and brachial artery pressure (below) with a high-fidelity Millar catheter in a patient during cardiac catheterisation at St Vincent's Hospital before (left) and immediately after (right) administration of glyceryl trinitrate sublingually. X denotes the initial wave generated in the ascending aorta by ventricular ejection. R is the reflected wave

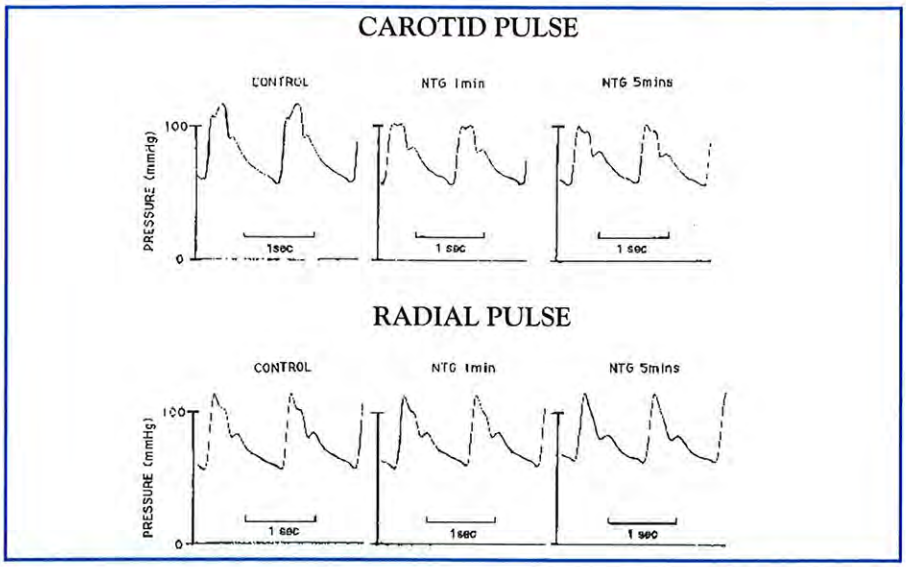


Figure 3. (b) Recordings of carotid artery pressure (above) and radial artery pressure (below) with a high-fidelity non-invasive Millar tonometer in a volunteer before (left) and after (centre and right) administration of nitroglycerine sublingually

Note that the change in pressure wave contour in the upper limb pulses are similar to those recorded by Murrell in 1879, and are associated with a substantial fall in central systolic pressure, but not systolic pressure where conventionally measured, in the brachial or radial artery

More recent work on the pulse was directed at developing a system for analysing the arterial pulse as recorded at the radial and carotid sites. We were able to show that wave transmission in the upper limb of humans, in contrast to wave transmission elsewhere, remains virtually constant at different ages and under different circumstances. Such findings permit the central (ascending aortic) pressure wave to be synthesized from the radial pulse at the wrist. Further analysis of the pulse permits expression of a host of indices which document the effects of wave reflection on the aortic pulse, and document the interaction between vascular load and cardiac contraction. The report that can be generated (Figure 4) is far more sophisticated and detailed than anything that has been available before, and is a major advance over the numbers measured by the sphygmomanometer alone, or the waves recorded directly by sphygmography or tonometry in a peripheral artery. Patent protection was sought for this process in the United States during 1988 and was granted in 1993. The U.S. patent is assigned to the American company which conceived and sponsored the initial work; this Company has an ongoing arrangement with the University of New South Wales. Currently, scientific and commercial developments in the United States are being pursued with a major East Coast university. Separately, an Australian company has developed an instrument (Figure 5), and has launched this in Australia, with plans for export in 1995.

The most recent work with this system, conducted at St Vincent's Clinic (and supported during 1993 by the Foundation) has been directed at validating the methods previously developed and exploring details as to how daily activities - sitting, standing, lying, eating, exercise, alter the arterial pulse and ventricular load. We believe that the system has special value in exploring the beneficial effects of vasodilator drugs, as used in treatment of hypertension, angina pectoris, and cardiac failure. Support for such studies has been sought from pharmaceutical companies. We believe too that the system will be better able to predict and evaluate the effects of exercise on the

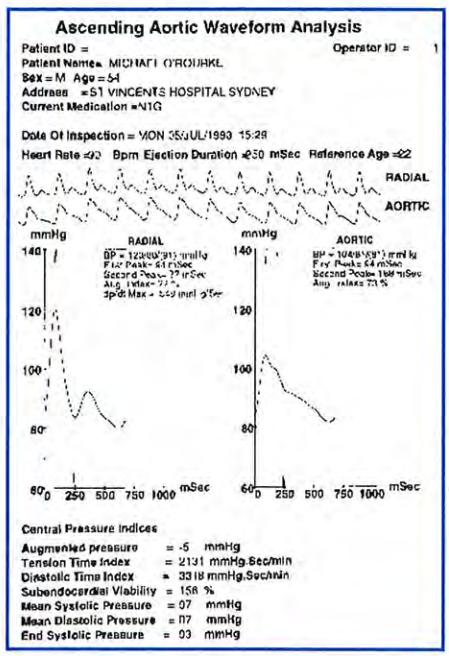


Figure 4. The detailed report generated from recording of pressure waves by applanation tonometry in the radial artery. The upper wave train is that recorded directly over 8 seconds in the radial artery while the lower wave train is that synthesised from the radial pulse; - in engineering terminology, using a convolutional algorithm derived from the generalised transfer function which describes wave transmission from ascending aorta to radial artery. The single wave at left is the ensemble-averaged radial wave, derived from the upper wave trace, and calibrated according to pressure recorded conventionally by sphygmomanometer. The single wave at right is the ensemble-averaged ascending aortic wave derived from the lower wave train.

Flags above and below the single waves identify the position of fluctuations on the wave and the beginning and end of ventricular ejection. Also shown are a variety of indices which quantify the effects of wave reflection, and the interaction between the left ventricle and whole circulation.

heart. Through use of the system, we believe we now have a probable explanation for the development of angina pectoris in some patients whose coronary arteries are normal or minimally narrowed, on the basis of relative difference in pressure maintained in the ascending aorta during systole and during diastole with exercise. Support for furtherance of this research was sought in 1993 and 1994 from the Clinic Foundation in association with the Department of Nuclear Medicine.

Perhaps the most exciting results of our work are yet to come, through explaining the development of cardiac failure in patients with increased vascular load and high peripheral wave reflection. To date we have concentrated on the effects of wave reflection as boosting systolic pressure and increasing load on the heart. We had not fully considered the theoretically valid concept that wave reflection can subtract from flow as well as adding to pressure. Preliminary data from patients with varying degrees of heart failure suggests that when the heart is weakened, wave reflection does subtract from flow, and so is responsible for the abbreviation of flow from the heart, the decrease in output from the heart, the impaired perfusion of bodily tissues, and the unusual pressure pulse in the radial artery that up until now we could not explain. If this concept can be verified, then inappropriate wave reflection will be established as the cause not only of increased pressure load, but of the ultimate heart failure which results from this. Therapy then can be targeted more appropriately in patients with cardiac failure. Studies are currently underway in this fascinating area, utilising both non-invasive studies on out-patients, and invasive studies in the diagnostic Cardiac Catheterisation department - the latter through Ray Kelly in conjunction with Associate Professor Michael Feneley. This new area will require better methods for measuring the arterial flow pulse then we have had available to date.

This work has progressed with the same focus on the same subject of arterial pulsations since Michael O'Rourke first met with Professor Michael Taylor at the Physiology Department at Sydney University in 1963, supported by a Little Shop grant from St Vincent's General Hospital. It has established our group as a world leader in this field of arterial hemodynamics, despite limited facilities. Clinical relevance is only now being fully appreciated; future potential has as few limits as when any new approach, any new technique, is launched into an important area such as that of cardiovascular disease. We acknowledge support from the Clinic Foundation in 1993, and hope to justify further support in years to come.

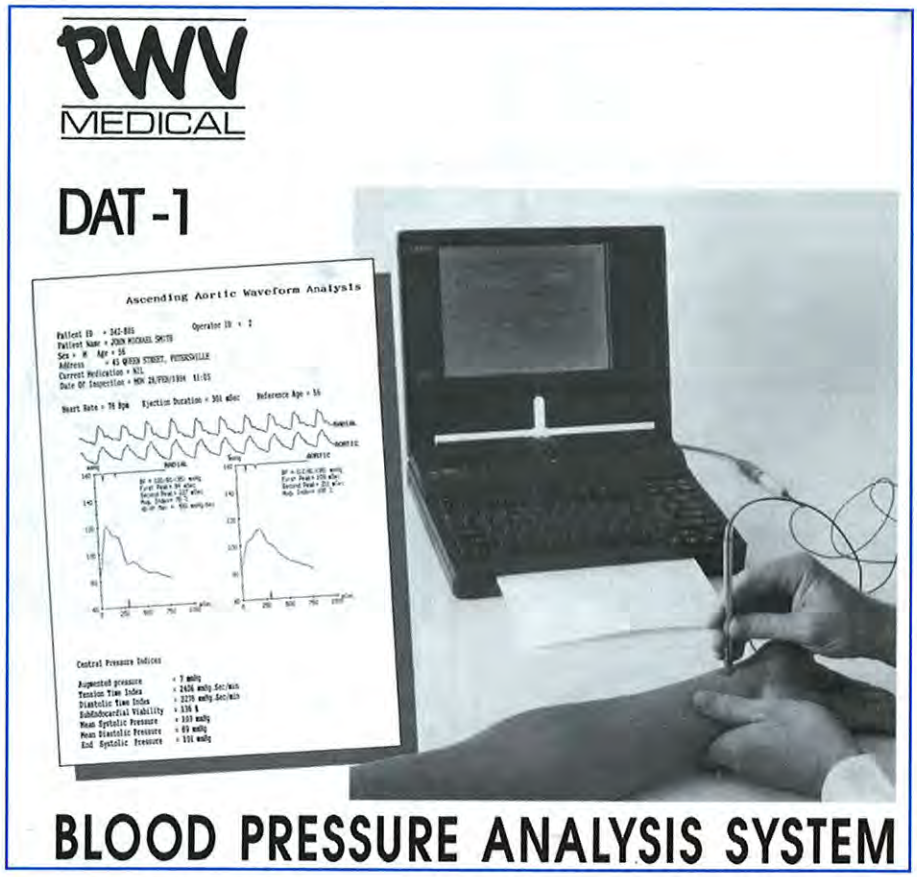


Figure 5. The blood pressure analysis system as developed for sale in Australia and overseas by PWV Medical, a Sydney-based company established in 1993

REFERENCES

1. Mackenzie J. The study of the pulse. London: Pentland 1902.
2. McDonald DA, Taylor MG. The hydrodynamics of the arteral circulation. Progress in Biophysics 1959;9:107-173.
3. SHEP. Implications of the systolic hypertension in the elderly program. Hypertension 1993;21:335-343.
4. Kelly RP, Hayward CS, Ganis J, Daley JE, Avolio AP, O'Rourke MF. Non-invasive registration of the arterial pressure pulse waveform using high-fidelity applanation tonometry. J Vasc Med & Biol 1:142-149, 1989.
5. Yaginuma T, Avolio AP, O'Rourke MF, Nichols WW, Morgan JJ, Roy PR, Baron DW, Branson J, Feneley MP. Effect of glyceryl trinitrate on peripheral arteries alters left ventricular hydraulic load in man. Cardiovasc Res 20:153-160, 1986.
6. Kelly RP, Hayward CS, Avolio AP, O'Rourke MF. Non-invasive determination of age-related changes in the human arterial pulse. Circulation 80:1652-1659, 1989.
7. Kelly RP, Gibbs HH, O'Rourke MF, Daley JE, Mang K, Morgan JJ, Avolio AP. Nitroglycerine has more favourable effects on left ventricular afterload than apparent from measurement of pressure in a peripheral artery. European Heart J 11:138-144, 1990.
8. Nichols WW, O'Rourke MF. McDonald's Blood Flow in Arteries, 3rd ed. London: Arnold 1990.
9. O'Rourke MF, Avolio AP, Kelly RP. The Arterial Pulse. Baltimore: Lea & Febiger, 1991.
10. O'Rourke MF, Kelly RP. Wave reflection in the systemic circulation, and its implication in ventricular function in man. (invited review). J Hypertension 11:327-337, 1993.
11. O'Rourke MF, Early thrombolytic treatment in acute coronary thrombosis. Aust NZ J Med 23:742-744, 1993.
12. Safar ME, O'Rourke MF. The arterial system in hypertension. Dordrecht Kluwer 1993.
13. Gallagher DE, O'Rourke MF, Kelly RP. Arterial stiffness and ventricular/vascular interaction. In: Vascular Medicine. Loscalzo J, Creager M, Dzau VJ (eds). Boston: Little Brown and Company, (in press) 1994.

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Thalamic Stimulation for the Control of Tremor of Parkinson's Disease

Chronic Thalamic Stimulation is a recently developed alternative treatment for patients with intractable tremor of Parkinson's Disease. St. Vincent's Hospital Sydney is the first Australian hospital to develop this technique and is part of the international trial of safety and reliability of the Medtronics Model 3387 Deep Brain Stimulation lead. It developed as a result of patients with Parkinson's Disease who have failed to respond adequately to medical treatment and who have persistent tremor. The technique of chronic thalamic stimulation has been developed by Professor Benabid, a neurosurgeon from Grenoble France [1]. At the time of writing three patients with severe unilateral tremor have undergone this procedure at St. Vincent's Hospital with complete cessation of tremor.

Background of the treatment of Parkinson's Disease

James Parkinson first described this disease back in 1817 and his description of the clinical features of the disease are still recognised as the ideal clinical behaviour of this disorder. It is fairly typical and easily recognised by most physicians and surgeons as a condition describing involuntary tremulous action with lessened muscular power in parts not in action and even when supported, with a propensity to bend the trunk forward and to pass from a walking to a running pace, the senses and the intellect being uninjured. That clinical description still holds today.

The diagnosis rests on certain criteria, namely bradykinesia which is slowness of initiation of voluntary movement with a progressive reduction in speed and amplitude to repetitive action. There is also at least one of the following: muscular rigidity, tremor and postural instability which is not caused by other neurological problems.

At the turn of the century at the National Hospital for Nervous Diseases in Queens Square, London, Gowers felt that of all the degenerative diseases of the nervous system, this was the least capable of arrest. On the surgical side it was Victor Horsley who first performed a cortical resection for hemiathetosis and Busey tried the procedure for Parkinson's Disease but this was unsuccessful. It was not until Speigel and others described their stereotactic encephalotome which

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enabled by stereotactic means to produce a lesion in the palatofugal fibres without causing paralysis in the patient that surgical treatment for Parkinson's Disease came to the fore. Irving Cooper in 1952, whilst performing an operation to produce a left pedunculectomy in a patient with post encephalitic Parkinson's Disease, the anterior choroidal artery was damaged and had to be clipped. This resulted in a complete alleviation of the tremor and rigidity in the contralateral extremities without actually causing any weakness in the patient. This was the beginning of surgical treatment of Parkinson's Disease. Cooper's studies showed that the optimal site was the ventro-lateral nucleus of the thalamus. He commenced cryogenic ventro-lateral thalamotomy for the control of Parkinson's Disease. It was around this time that the Neurosurgical Department at St. Vincent's Hospital became involved in treatment of Parkinson's Disease in the later 1950s and early 1960s. The pioneer of this work at St. Vincent's was Dr Kevin Bleasel. During the 1960s right through to the early 1970s frequent thalamotomies were performed for the treatment of Parkinson's Disease.

Research at this stage discovered that the brains of patients dying of Parkinson's Disease were deficient in Dopamine. The obvious response to this was to try Levodopa which is the precursor for Dopamine and the initial response was poor, but subsequently with modification, prolonged doses of Levodopa became beneficial in the late 1960s and into the early 1970s. It was first used at St Vincent's Hospital in 1970. At that stage, surgery virtually went into oblivion apart from the occasional patient having a thalamotomy for a severe tremor. On the average, even at The Queens Square Hospital in London, they would only be doing two to six operations in any one year.

However over the last 15 to 20 years for which Levodopa has been used for the treatment of Parkinson's Disease there have been long term problems. There has been decreased control of Parkinsonian symptoms, increased involuntary movements, alteration in mentation, increasing fluctuations, the patient having freezing episodes with increasing fatigue. It is mainly at the decreased control of the Parkinsonian symptoms, particularly the severe tremor of these patients, that surgery has been resurrected. As a consequence there have been a lot of studies done experimentally by Professor Benabid in his unit in Grenoble. In his research laboratory, monkeys in whom he has induced tremor, he has developed the technique of thalamic stimulation. This is a fairly revolutionary technique but as most surgeons would do prior to producing a thalamotomy, they would stimulate the site to abolish the tremor before actually making the lesion. This led to the concept of prolonged stimulation for Parkinson's Disease and he commenced his work in 1987. He first published his work on 26 patients in 1991 in the Lancet [1] and recently in Rome presented his series of 130 patients all of whom have been successful in control of tremor. The technique is similar to thalamotomy. An electrode is passed down into the thalamus and via an electrode run subcutaneously under the skin into a pacemaker (Figure 1). The pacemaker is then programmed to give certain stimulation rate usually in the order of three to four volts, at a pulse with 60 micro seconds and around 160 hertz. While the stimulation is on, the patient has no tremor. The patient can then turn the pacemaker off with a magnet particularly at night and this saves the battery and prevents the development of tolerance. The ITREL (Medtronics) Pacemaker which is similar to a cardiac pacemaker can be used on either bipolar or monopolar stimulation. A computer is used to program the pacemaker in the patient after surgery has been completed.

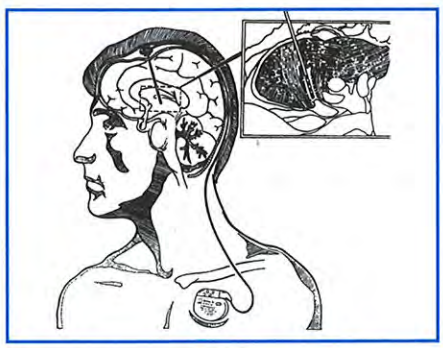

Figure 1. Diagrammatic representation of chronic thalamic stimulation

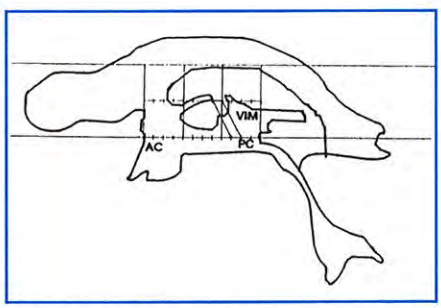

Figure 2. Guiot diagram for the localization of the VIM Nucleus

OPERATIVE TECHNIQUE

The Ventral intermedius nucleus (VIM) is the target to be stimulated or destroyed by thalamotomy and different procedures exist for the localization of the anatomical target. The hallmark throughout the years in finding the target is a line drawn between the anterior commissure and the posterior commissure and the target is found according to the construction of Guiot [1] (Figure 2). Before modern imaging, this

was all done on ventriculography but currently at St. Vincent's Hospital the MRI scanner is used because on a sagittal MR image the anterior commissure and the posterior commissure can be directly visualized and the line drawn between them [2] (Figure 3). The VIM nucleus is identified by measurement from the posterior commissure; that is 3/12ths of the distance of the anterior commissure-posterior commissure line. The typical lateral position of the VIM varies between 13.5 millimetres (for normal brain) and 16 millimetres or more (for brains with an enlarged IIIrd ventricle) from the midline of the brain. The laterality depends on the width of the IIIrd ventricle.

The procedure is done under local anaesthetic so the abolition of tremor with stimulation can be assessed. The MRI intermediate localizer (Radionics) is inserted under local anaesthetic and fixed to the skull by four pin fixation. MRI scans are then performed and the target calculated by the above technique. The patient is returned to theatre where the CRW Stereotactic apparatus (Radionics) is connected to the MRI intermediate ring and the area draped for surgery. An incision is made adjacent to the midline in the region of the coronal suture. A curvilinear incision is made and a small twist drill burr hole, the diameter of 1/8" is made and the dura then pierced. A canula is then inserted down to the coordinates that have been chosen for the target. It is inserted in an incremental fashion starting about 10 millimetres before the chosen target and extending down in an incremental fashion of three millimetre separation to the target so the best site of stimulation can be achieved. Physiological stimulation is important to verify the anatomical localization. At each distance from the target the area is stimulated and using the Radionics Radiofrequency Lesion Generator a test stimulation is made (Figure 4). This is used to ascertain whether there is abolition of tremor without side effects. The electrode is advanced two millimetres beyond the target and stimulated to determine the best of tremor abolition and where the least side effects such as paraesthesia might occur. The target that gives the best cessation of tremor and the least side effects is chosen for the placement of the implanted electrode.

A quadripolar Medtronic electrode is inserted. At the tip of the electrode there are four stimulating areas which can be used in unipolar or bipolar mode (Figure 5). This has the advantage that the electrode which gives the best stimulation can be chosen for the chronic pacing. If this is not the first electrode then the second or third electrode can be used. The electrode is implanted through the canula, the canula withdrawn and the electrode inserted subcutaneously under the skin connected to the external electrode. At the second procedure some days later, the electrode is connected to the pacemaker box which is placed in the infraclavicular region (Figure 6). The electrode is not connected to the internal pacemaker at the first operation because of a microthalamotomy effect from passage of the electrode and also with the external lead the best perimeters for control of tremor can be ascertained.

Discussion

The neurosurgical treatment of choice for disabling, drug resistant tremor has been ventral intermediate nucleus (VIM) thalamotomy [2][3]. However tremor occurs in about 20% of cases [4], there are significant adverse effects [5] and the risks are compounded when the procedure is done bilaterally [6].

Where thalamotomy is performed, anatomical localization is achieved with ventriculography, CT or MRI. Physiological confirmation of the correct target site for thalamotomy is performed intraoperatively prior to the destructive lesion being made. Since the ventral intermediate nucleus is surrounded by the internal capsule, thalamic nuclei (the dorso lateral and ventro medial complex), and red and subthalamic nuclei, an error in coordinates may cause severe post operative complications such as speech, gait and movement disorders.

Acute intraoperative VIM stimulation arrests tremor [7]. Professor Benabid and his co-workers initiated study on chronic thalamic stimulation other than to perform a destructive lesion. Previously, chronic thalamic stimulation with deep brain stimulating electrodes had been used safely in the treatment of intractable pain for more than 25 years. Benabid and his co-workers [7] implanted a stereotactic high frequency device in the VIM nucleus to control Parkinsonian tremor and obtained good results in their patients. They reported two years later that the favourable effect of chronic thalamic stimulation seemed to be maintained over the long term [8]. A similar technique was proposed by Blond and Seigfried [9] who emphasized the reversibility of the surgical procedure.

Figure 3. Sagittal MRI scan showing the AC-PC line

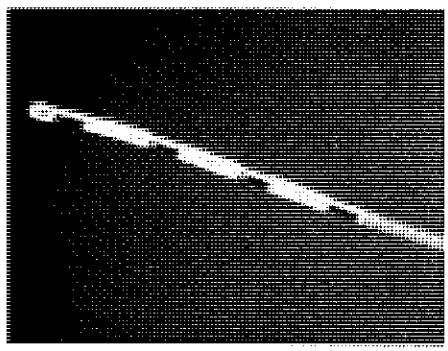

Figure 5. The Quadripolar Medtronics electrode

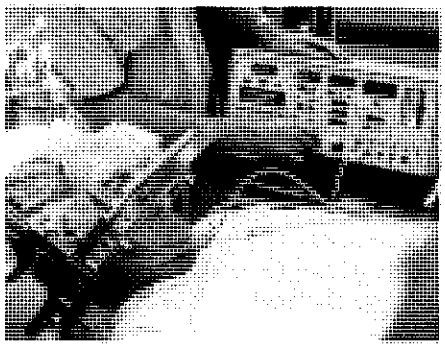

Figure 4. The stimulating electrode is passed to the VIM Nucleus under local anaesthesia and a test stimulation made

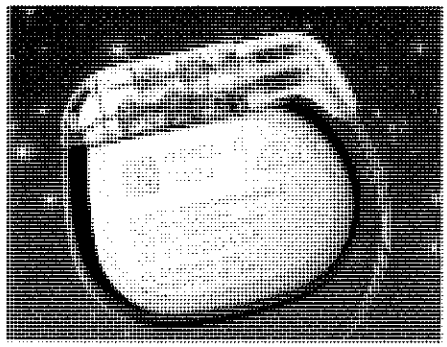

Figure 6. The ITREL Pacemaker box

Strength-Weakness-Opportunity-Threat analysis (SWOT analysis) for Thalamotomy and DBS

Thalamotomy		Deep Brain Stimulation	
Strength: Extended experience in the medical community. Shorter procedure than for DBS. If no permanent side effects, the efficacy is high.	Opportunities: If no permanent side effects, the costs are lower than for DBS. Improved technology may reduce the risks to an even lower level.	Strength: Essentially reversible procedure. Bilateral treatment possible without permanent additional side effects. Bilateral implant in the same surgical procedure is not contra-indicated Post operative adjustments of the physiological effects can be made non-invasively.	Opportunities: Implant procedure virtually identical to the thalamotomy procedure; risks are well known. The fundamental opportunity for neuro-modualtion.
Weakness: No bilateral treatment possible. Fundamental aversion of patients against destruction of part of the brain. No procedure exist to determine the minimum size for a long term, physiologically effective thalamotomy.	Threat: Chances for irreversible severe neurological deficits larger than for DBS.	Weakness: Permanent implant of foreign bodies (IPG, lead) is required. A replacement of the current design simulator is required about every 4 years but can be done in an out-patient clinic. The initial implant requires more surgical interventions than for a thalamotomy.	Threat: Non-sufficient scientific proof that DBS is preferred over thalamotomy: A comparitive DBS versus Thalamotomy study is missing. Missing cost-effectiveness study for DBS, thalamotomy and medical treatment.

Table 1.

In a report to the Lancet, Professor Benabid [1] described the usefulness of high frequency stimulation (ie at 100 hertz or more) of the VIM as the first neurosurgical procedure in disabling tremor in 26 patients with Parkinson's Disease and six with essential tremor. Seven of these patients had already undergone thalamotomy contralateral to the stimulated site and 11 others had bilateral VIM stimulation at the same time. Chronic stimulating electrodes connecting to a pulse generator were implanted in the VIM. Of the 43 thalamii stimulated, 27 showed complete relief from tremor, and 11 major improvement (88%). The improvement was maintained for up to 29 months (mean follow-up 13 months). Adverse effects were mild; there were paraesthesiae in three cases, dystonia in two, gait disorders in four and dysarthria in seven. These adverse effects could be eradicated by the reduction or cessation of stimulation.

Thalamic stimulation seems to induce less adverse effects than destructive thalamotomy, particularly when bilateral [6][10]. Dysarthria and dysequilibrium still occur, but the patient is able to control them by reducing the intensity of the stimulation. The functional nature of the stimulation which makes all the effects induced reversible, is the principal advantage of this technique over the permanent technique of thalamotomy. Unilateral stimulation gives about the same beneficial and adverse effects as unilateral thalamotomy but thalamic stimulation is preferable because it can be carried out in the elderly or severely affected patient without major risk [1] (Table 1). The adaptability of thalamic stimulation in the long term will allow small adjustments of electrical intensity according to the spontaneous evolution of the disease and changes in drug treatment.

The mechanism of action of chronic VIM stimulation is not known and alteration or functional ablation of the discharging system has been suggested [9][11]. Ventral thalamic nuclei appear to be the last relays of complex neuronal loops which finally project to the motor and premotor cortex. Electrical stimulation could inhibit the neuronal rhythmic firing of the transcortical reflex loop passing through VIM [1].

Conclusion

Stereotactic thalamic stimulation appears to be a safer procedure than traditional destructive thalamotomy; neurological damage is less frequent and there are fewer side effects. The advantages of reversibility and adaptability of chronic VIM stimulation should make the procedure preferable to traditional thalamotomy especially when bilateral surgery in indicated.

The Neurology and Neurosurgical departments of St. Vincent's Hospital plan to perform at lease six procedures a year using this revolutionary method of treatment of tremor of Parkinson's Disease.

References:

1. Benabid AL, Pollak P, Gervanson C et al. Long term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 1991; 337: 403-6
2. Andrew J Surgical treatment of tremor. In: Findley LJ, Capildeo R eds. Movement disorders: tremor. London: Macmillan, 1984: 339-51
3. Narabayashi H. Stereotaxic Vim thalamotomy for treatment of tremor Eur Neurol 1989: 29 (suppl 1): 29-32
4. Hirai T, Miyazaki M, Nakajima H, Shibazaki T, Chye C. The correlation between tremor characteristics and the predicted volume of effective lesions in stereotactic nucleus ventralis intermedius thalamotomy. Brian 1983; 106: 1001-18
5. Tasker RR, Siqueira J, Hawrylyshyn P, Organ LW. What happened to VIM thalamotomy for Parkinson's Disease. Applied Neurophysicol 1983: 46: 68-83
6. Matsumoto K, Asano T, Baba T, Miyamoto T, Ohmoto T. Long term follow-up results of bilateral thalamotomy for Parkinsonism. Applied Neurophysiol 1977; 39: 257-60
7. Benabid AL, Pollak P, Louveau A et al: Combined (thalamotomy and stimulation) stereotactic surgery of the Vim thalamic nucleus for bilateral Parkinson disease. Applied Neurophysiol 1987; 50: 344-346
8. Benabid AL, Pollak P, Hommel M et al: Traitment du tremblement parkinsonien par stimulation chronique du noyau ventral intermedaire du thalamus. Rev. Neurol 1989; 145:320-323
9. Blond S, Siegfried J : Thalamic stimulation for the treatment of tremor and other motor movement disorders. Acta Neurochir Suppl. 1991; 52: 109-111
10. Cooper 15. Neurosurgical treatment of the dyskinesias. Clinical Neurosurgery 1977; 24: 367-390
11. Blond S, Cararros - Lefebure D, Parker F et al: Control of tremor and involuntary movement disorders by chronic stereotactic stimulation of the ventral intermediate thalamic nucleus. J Neurosurg 1992; 77: 62-68

Dr Janet Rimmer

Asthma - Current Trends

Abstract

Asthma is an increasingly common disease affecting 10-15% of our population. It represents significant morbidity, mortality and cost to our community.

Recent research has emphasised the importance of bronchial inflammation in the pathogenesis of asthma. Elucidation of this process continues and shows that lymphocytes, eosinophils and mast cells all play significant roles.While the precise causes of asthma are still unknown current knowledge increases at a rapid rate making this a very exciting field.

The recognition of the underlying inflammatory process has in turn led to increased emphasis on prophylactic treatment (inhaled corticosteroids and sodium cromoglycate) and a more cautious use of B-agonists. Australia has been one of the first countries to introduce a National Asthma Campaign and promotion of individual Asthma Management Plans which may have contributed to recent falls in mortality.

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Asthma is a common condition, recent trends showing an increase both in the prevalence and morbidity of asthma. It has been estimated that 1.4 million Australians are affected by asthma with a total cost burden to the Australian community of approximately 600 million dollars [1].

Definition

Recent definitions of asthma recognise for the first time the importance of airways inflammation in asthma [2]. Hence asthma can be defined as having the following characteristics:

(1) Recurrent episodes of airways obstruction that are reversible (but not completely in some patients) either spontaneously or with treatment.

(2) Airways inflammation.

(3) Increased airway responsiveness to a variety of stimuli.

Recurrent episodes of airways obstruction are characterised by symptoms of wheeze, chest tightness, dyspnoea and cough which can be productive.

The presence of airways obstruction is measured by the reduction in FEV1 (spirometer) or peak flow rate (peak flow meter); these parameters reflect the

Clinical Classifaction of Asthma

TITLE	DESCRIPTION
Current persistent asthma (subgroups mild/moderate/severe)	Regular symptoms and treatment in last 12 months
Episodic asthma	2 months symptoms free period, treatment up to once per year
Past asthma	Regular treatment for 12 months, nil in last year
Current trivial wheeze	No treatment
Potential asthma	+ve bronchial provocation challenge, no symptoms

Table 1.

calibre of large airways and, if normal, a flow volume curve is necessary to detect flow limitation in smaller airways. Asthmatics are strongly encouraged to keep regular peak flow diaries as part of their management particularly as patients often display a poor perception of their symptoms [3].

Asthma has been traditionally divided into intrinsic and extrinsic subtypes depending on the demonstration of atopy. A more comprehensive clinical subclassification includes current persistent asthma, episodic asthma, past asthma, current trivial wheeze and potential asthma (see Table 1).

Airway Hyper-responsiveness (AHR)

The majority of asthmatics display airway hyperresponsiveness which is an exaggerated constrictor response to a wide range of challenges which include exercise, cold dry air, methacholine, histamine, hypertonic saline and sulphur dioxide. Asthmatics are 10 to 1000 fold more responsive to inhaled histamine and methacholine than normals.The extent of this hyperreactivity correlates with the clinical severity of the condition and need for treatment [4]. However AHR is not synonymous with asthma as it is present in other lung conditions such as chronic bronchitis, bronchiectasis, sarcoidosis and post heart-lung transplantation [5][6][7] as well as approximately 5% of asymptomatic subjects [8]. In addition treated asthmatics may no longer demonstrate AHR.

The most common methods of demonstrating AHR are a histamine or methacholine bronchoprovocation test in which the subject inhales increasing doses of histamine (0.03-3.9umol) until either a 20% fall in FEV1 results or the top dose is inhaled. The provocative concentration to produce a 20% fall in FEV1 is expressed as the PC20. Other parameters which are obtained from this curve are the dose response ratio (DRR = maximal % fall FEV1/total dose) and the plateau or maximum achievable bronchoconstrictor response. Normals have a demonstrable plateau but this is often absent in asthmatics. Widespread application of this technique has suggested that asthmatics can be divided into mild, moderate and severe categories on the basis of their PC20 (Figure 1).

AHR is distributed continuously in the population and hyperresponsiveness is defined arbitrarily as a PC20<4umol, therefore a proportion of apparent normals will demonstrate mild BHR. Similarly some asthmatics will not have AHR and this may be as high as 40-70% in children [9][10]. Airway challenge tests show low sensitivity, high specificity and a high negative predictive value for diagnosed asthma. The results of these tests therefore must be interpreted in the clinical context.

Pathology of Asthma

In the last 10 years there have been numerous studies of bronchial biopsies in mild to moderately severe asthmatics. Comparison between asthmatics and normals have uniformly indicated the presence of bronchial inflammation in asthmatics (Figures 2 and 3). Characteristic pathology includes disruption of bronchial epithelium with the presence of intraluminal debris (Charcot Leyden crystals, creola bodies, Curschmann's spirals, mucoid secretions and inflammatory cells). Extending from

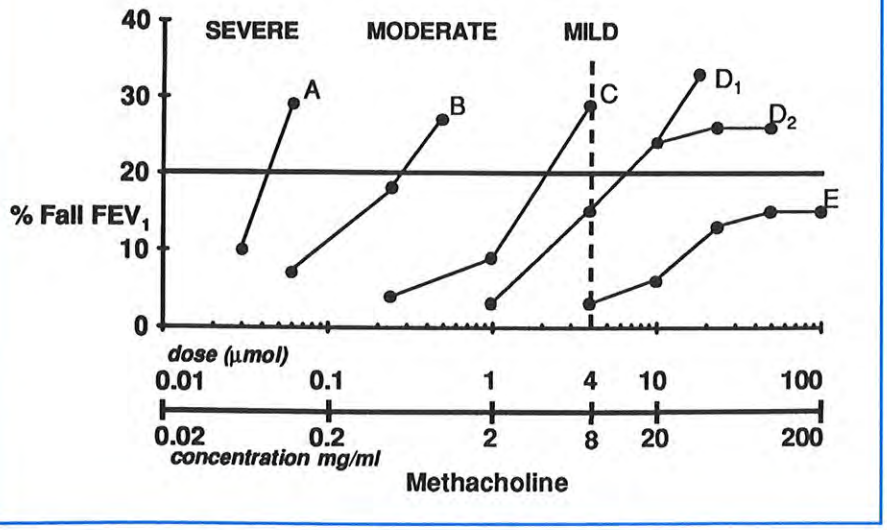

Figure 1. Airway responsiveness in severe (A), moderate (B), mild (C) asthmatics, atopic rhinitis with (D1) and without (D2) a plateau and normals (E)

Figure 2. Airway wall cross-section from a subject with clinically severe asthma. Note the loss of columar epithelial cells (E), thick basement membrane (BM) and numerous inflammatory cells in the airway wall (arrow)

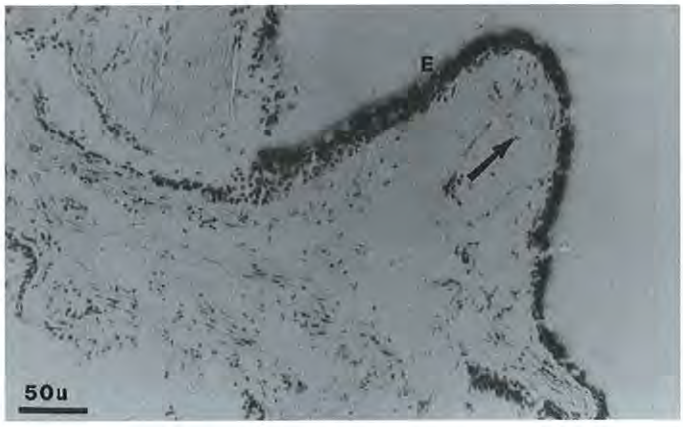

Figure 3. Airway cross-section from a subject with no respiratory illness. Ciliated pseudostratified columar epithelium is intact (E). Occasional lymphocytes are present in the lmaina propria(arrow)

the bronchial epithelium through the muscle layer and into the submucosa is an inflammatory cell infiltrate comprised primarily of lymphocytes but also eosinophils and mast cells. The basement membrane is thickened due to sub-basement membrane deposition of collagen types 1,3,4 and fibronectin, the types most likely to derive from fibroblasts [11]. This may be laid down by a recently described cell, the myofibroblast, as a response to epithelial injury [12].

A combination of biospy and bronchoalveolar lavage (BAL) studies have demonstrated that all the involved cell types are activated with increased expression of cell surface markers, increased release of mediators and the potential to produce cytokines.

BAL studies in asthma show no increase in the total cell count but an alteration in the differential count with increased eosinophils, mast cells, lymphocytes and epithelial cells.

Inflammatory cells in asthma

Present evidence indicates that inflammation in asthma is a complex multicellular event involving eosinophils, lymphocytes, mast cells and a vast array of mediators and cytokines. While most research has examined atopic or allergic asthmatics studies suggest that a similar process occurs in intrinsic and occupational asthma.

Eosinophils: The importance of eosinophils in asthma is underlined by an alternative description of asthma as "chronic eosinophil desquamative bronchitis." In normal subjects eosinophils usually comprise less than 5%(<250 per mm3) of peripheral blood cells, yet in asthmatics increases in eosinophils numbers can be shown in blood, sputum, BAL and bronchial biopsies. Following an allergen bronchoprovocation challenge blood eosinophil counts fall (9hrs), then increase (24hrs); the increase is derived from the bone marrow as circulating eosinophil/basophil progenitors increase at the same time. These eosinophils migrate into the bronchi as eosinophil BAL numbers also increase. The method of selective eosinophil migration at sites of mucosal inflammation involves upregulation of adhesion molecules on both eosinophils and capillary endothelial cells. Following capillary endothelial cell adherence, eosinophils diapedese through the vascular endothelium and migrate to the site of inflammation under the influence of a chemotactic gradient. Three families of adhesion molecules have been implicated in eosinophil migration: the selectin family, integrin family and the immunoglobulin superfamily. Differences in adhesion molecules and response to chemotactic stimuli result in an eosinophilic rather than neutrophilic infiltrate [13]. The expression of adhesion molecules is upregulated by various cytokines.

These eosinophils are activated by morphological criteria (reverse core density indicating loss of major basic protein - MBP), reduced density indicating degranulation, increased metabolic activity and receptor expression.

At one stage considered to be a benign cell, the eosinophil is probably responsible for much of the bronchial epithelial damage. Eosinophil granules contain basic proteins such as MBP, eosinophilic cationic protein (ECP), eosinophil derived neurotoxin (EDN), eosinophil peroxidase and generate oxygen free radicals all of which can contribute to epithelial cell lysis and detachment, as well PAF and LTC4 cause bronchoconstriction, mucous secretion and microvascular leakage.

Bronchial Epithelial Cells: Increased numbers of bronchial epithelial cells are recovered from the sputum and BAL of asthmatics. Although this may be a consequence of the asthmatic inflammatory process it may also contribute to the pathogenesis of asthma. Hence this loss of a protective barrier results in increased exposure of sensory nerve endings, increased epithelial permeability allowing easier access of allergen and decreased production of epithelial derived relaxant factors [14][15]. The shedding of epithelial cells appears to occur at the epithelial/basal cell plane with clusters of epithelial cells identifiable in BAL. This pattern of injury has been shown, in vitro, to occur due to MBP exposure [16]. Of interest is the increased bronchial epithelial cell expression of ICAM-1 an adhesion receptor which is also a receptor for the rhinovirus suggesting a link between viral infections and asthma exacerbations.

Lymphocytes: These are the most numerous cells in the asthmatic bronchial mucosa and considerable evidence suggests that they are vital in the initiation and maintenance of the

allergic inflammatory response involving IgE production, mast cell and eosinophil chemotaxis, activation and persistence [17]. These lymphocytes are mainly Th2 (CD4+, helper T) cells which produce a particular proallergic cytokine profile (IL3,4,5,6,10,GMCSF,TNFa).

These lymphocytes are activated as determined by expression of cell surface activation markers such as the interleukin 2 receptor (IL2R or CD25), the type 11 histocompatability antigen (HLADR) and very late antigen (VLA) and have an enhanced capacity to produce cytokines. A correlation between CD4+ bronchial lymphocytes, IL5 production and eosinophils has led to the hypothesis that lymphocytes orchestrate the influx and activation of eosinophils [18].

Development of assays to measure cytokine levels has now shown increased levels of GMCSF,IFg,IL2-R,IL5,IFNg in blood and IL1B,IL6,GMCSF,TNFa,IL2 in BAL of asthmatics compared to controls.

Mast Cells: Mast cells contain histamine and consequently have always been accorded a prominent role in many allergic reactions. In asthma histamine is dominant in the early phase of the Type 1 allergic response, producing about 50% of the bronchoconstriction; it has a much lesser role in the Type 1 late phase response. In addition to histamine, mast cells produce numerous other mediators including leukotrienes (previously called the slow reacting substance of anaphylaxis), prostaglandins, heparin, platelet activating factor, adenosine, chemotactic factors, proteases such as tryptase and cytokines. Mast cell numbers are increased in the BAL and bronchial biopsies of asthmatics. Both mast cells and their circulating counterpart the basophil display evidence of activation [19] indicated by increased mediator releasability and elevated mediator levels (histamine and tryptase) in BAL. Lymphocytes promote proliferation and maturation of mast cells by production of IL3,IL4,IL5 and also promote mast cell degranulation via the release of histamine releasing factors; in turn mast cells possibly store cytokines (IL3,IL4,IL5) which may act in a paracrine or autocrine fashion [20].

Relationship between bronchial inflammation and AHR

Airway inflammation expressed as cell numbers has been shown to occur without AHR in idiopathic eosinophilia, transplant rejection and some subjects with persistent cough [21][22][23][24][25]. Conversly AHR may occur without airway inflammation [26][27].

As not all studies have demonstrated a significant relationship between cell numbers (BAL, biopsy or sputum) and AHR so the focus has shifted to the level of cell activation and involvement of multiple cell types rather than cell numbers alone.

A number of different markers have undergone preliminary evaluation including histamine releasability, lymphocyte surface markers, eosinophil numbers and serum ECP. Most when measured in the blood are insufficiently sensitive and specific to distinguish between asthmatics and controls; perhaps the most promising is that of serum ECP (a released eosinophil granule product). However, our own studies indicate that serum ECP does not distinguish between different clinical groups (nonatopic controls, atopic nonasthmatics and atopic asthmatics) [28] although serial measurements may be useful in individual cases [29].

Alterations in bronchial inflammation have been conclusively demonstrated after both allergen challenge and inhaled corticosteroid therapy and associated with these changes has been an alteration in AHR. The size of the change in AHR suggests that these inflammatory changes are responsible for some but not all AHR. Therefore "nonalterable inflammatory factors" and other mechanisms are responsible for AHR; the latter may be due to altered mechanical properties of the airways such as subbasement membrane thickening or altered elastic recoil.

Other causes of Asthma

While much of the current attention is centred on the role of inflammation as a cause of asthma other factors may also be important.

(a) Airway geometry: Airway narrowing is caused by multiple factors including mucosal oedema, luminal secretions and bronchial smooth muscle hypertrophy. As airway resistance is proportional to the inverse of the fourth power of the radius a small reduction in airways diameter will cause a large increase in resistance. Indeed, a close correlation between BHR and baseline airway calibre (FEV1) has been found in chronic obstructive pulmonary disease but the relationship is less evident in asthma. Airway wall thickening may have little effect on baseline lung function but could markedly increase airway responsiveness, thus linking the presence of airway inflammation and AHR [30].

(b) Microvascular leakage is also present in asthma and can be detected as increased levels of serum proteins in sputum and BAL. Leakage occurs at postcapillary venules and inflammatory mediators such as histamine, bradykinin, leukotrienes and PAF are all capable of causing leakage by contracting endothelial cells allowing extravastion of macromolecules. The consequences of microvascular leak include oedema of the airways, epithelial desquamation, formation of mucous plugs, interference with mucociliary clearance and a source of bronchospastic kinins. However the relative importance of microvascular leak in asthma is not known.

(c) Airway smooth muscle: as asthmatics display increased AHR or muscle twitchiness it seems logical that there is an abnormality of airway smooth muscle. Much effort has been expended, but no definite abnormalities have been found. Certainly there appears to be an increased amount of airway smooth muscle present but it is not known whether this represents hypertrophy, hyperplasia or both in muscle cells. No relationship has been demonstrated between in vivo and in vitro responsiveness of airway smooth muscle to either histamine or acetylcholine. However sensitised muscle is more reactive to histamine than nonsensitised tissue indicating a possible interaction between atopy and AHR; the mechanism for this is unknown.[31]. Conduction or biochemical abnormalities of airway smooth muscle have been postulated but as yet not demonstrated definitively.

(d) Nervous system: Autonomic control of the airways involves cholinergic, adrenergic and nonadrenergic, noncholinergic (NANC) systems. An overall imbalance of the excitatory and inhibitory components of these systems is postulated in asthma. Pharmacological and immunohistocytochemistry data tends to support this hypothesis [32]. There is likely to be a close relationship between airway inflammatory cells and neuropeptides.

(e) Genetics: The role of genetics in asthma is felt to influence both the development of atopy and asthma. Recent studies have suggested an autosomal dominant mode of inheritance of atopy, located on chromosome 11q [33]; however these data have been difficult to reproduce.

A genetic association for asthma independent of atopy is also postulated but has not yet been identified. A recent Australian study of monozygotic twins has calculated that only 69% of the variance is explained by genes; the remaining 31% is attributable to differences in environment and in this regard differences in total serum IgE and indoor allergen exposure are important [34].

(f) Environment: Alterations in asthma prevalence following migration indicate the importance of local environment in the development of asthma. There is a lower prevalence of asthma in black children of West Indian origin born in the West Indies compared with those born in London. Similar studies in Australia show that amongst Asians the prevalence of asthma is low but following immigration to Australia increases with the length of stay; it is postulated that dust mite exposure is a significant risk factor for the development of asthma [35].

Cigarette smoking is associated with independently increased risks of AHR and an elevated serum IgE [36]. Post-natal tobacco smoke exposure predisposes to respiratory infections and the development of allergic disease [37]. In subjects with chronic bronchitis and AHR altered geometry of the airways is likely to be important, as AHR correlates with baseline lung function.

Pollutants include both outdoor, derived from industry emissions and car exhaust such as SO2, NO2, ozone and particulate matter, and indoor, including cigarette smoke,NO2 from gas stoves and formaldehyde from painted furniture. Exposure to pollution increases the incidence of atopy [38]. The reunification of Germany has enabled a recent study to compare the frequency of wheeze between more and less polluted regions; surprisingly the prevalence of asthma and atopy was higher in the less polluted regions of West Germany [39].

House Dust Mite Exposure and Asthma Risk

	Relative Risk
Asthma in atopic child	15
Lung cancer in a smoker	8-20
IHD in male, chol>6mmol/L	3

Table 2.

In the *diet* certain foods can trigger asthma either by a direct IgE mediated repsonse or a pharmacological response to substances such as acetylsalicylic acid, monosodium glutamate, presevatives such as sodium metabisulphite and food colourings such as tartrazine. The latter response is more common although the precise prevalence is unclear. It would seem that ingestion of these food additives can trigger an acute attack of asthma but does not increase the AHR. Dietary manipulation which should include double blind testing can benefit a small proportion of asthmatics.

An association between dietary salt intake and AHR has been demonstrated but the reason for this is unknown [40].

The role of *allergens* is discussed below, but it is relevant to note that in some cases inhalant allergens have caused local epidemics of asthma. In Barcelona exposure to soya bean dust was responsible for several epidemics of asthma [41], moulds and grass pollens have been identified especially in relation to weather changes [42][43][51].

Viral infections can induce transient and increased AHR in normals and asthmatics respectively and presumably virally induced airway inflammation is responsible [44]. Historically, exacerbations of asthma are often preceded by a respiratory viral infection and this has been confirmed with modern techniques better able to demonstrate the presence of viral infection.

In infancy RSV bronchiolitis may predispose to the development of asthma [45] although other studies suggest that the infection merely causes onset of wheezing in a predisposed infant.

Allergy and Asthma

In the majority of asthmatics allergen sensitisation is the most important aetiological factor in the development of asthma with over 90% of children and 50% of adults with asthma demonstrating allergen sensitisation.

How does inhaled allergen result ultimately in bronchial inflammation? This requires two steps: the initial sensitisation process, assumed to occur early in life, and subsequent repeated challenge situations.

Evidence suggests that sensitisation to allergens involves an interreaction between antigen, antigen presenting cells and T-lymphocytes, and occurs in genetically predisposed individuals [46]. Environmental factors such as allergen potency, timing and concentration of exposure and the presence of adjuvant factors also influence the sensitisation process. Intense and early exposure to dust mite allergen is a risk for sensitisation and the development of asthma. A threshold level of exposure to >2ug/g of dust mite allergen (Der p1) (equivalent to 100 mites/g dust) is a risk factor for sensitisation while >10ug/g Der p1 is a threshold level for the development of acute allergic symptoms [47]. Indeed sensitisation is significantly associated with recent asthma, hayfever, eczema and AHR, with house dust mite sensitivity having the strongest association with current asthma [48]. Acute severe attacks of asthma also correlate with sensitisation to inhalant allergens [49]. House dust mite exposure as a risk factor for the development of asthma can be best appreciated when compared to other well known and accepted risk factors such as smoking and lung cancer, hypercholesterolemia and ischaemic heart disease (Table 2),[50].

A large number of studies have used a laboratory model of inhaled allergen aerosol which results in a Type I allergic response with early and late increases in airways obstruction and development of increased BHR. These studies, although not mimicking natural allergen exposure, have demonstrated without doubt the influx of inflammatory cells and associated release of mediators which cause smooth muscle contraction,mucous secretion, oedema, plasma leakage, neural activation, tissue damage and increased AHR. Use of pharmacological blocking agents has shown that 50% of the airways obstruction in the early asthmatic reaction is attributable to histamine and the rest due to the combined effects of prostaglandins, leukotrienes and other mediators. There has been intense interest in the late asthmatic reaction as it is associated with the development of increased AHR. During the late asthmatic reaction there is increased airway inflammation which has resulted in the hypothesis that airway inflammation causes AHR. Closer examination of this relationship shows that the increase in AHR after an allergen challenge actually precedes the onset of the late asthmatic reaction; in other words these two events occur in parallel and although both may be related to the presence of airway inflammation they each relate to different aspects of airway inflammation.

One theoretical problem with natural allergen challenge has been the putative size of the inhaled particles which are too large to penetrate into the bronchial tree. However bronchial inflammation has been shown to follow natural or seasonal exposure to grass pollens implying that allergen accesses the bronchial tree. A recent study shows that under appropriate weather conditions rye grass pollen grains approximately 35 microns in diameter will release submicronic particles small enough (<5 microns in diameter) to be inhaled and that these particles are still allergenic [51]. Dust mite faecal particles, which are the source of dust mite allergen, are somewhat larger (10 - 20 microns) but a small percentage exist in the respirable size range. Dust mites produce 5 - 6 major allergens including Der p1 and some of these have been characterised. Interestingly most of these have enzymic activity which may facilitate interaction between the allergen and the host. Der p1 has been shown to increase epithelial permeability, induce epithelial cell detachment and release cytokines [52][53]. These enzymic rather than allergenic properties of house dust mite may explain the AHR demonstrated in one month old infants exposed to high levels of Der p1 in their bedding.[54].

While allergen exposure does not explain the triggering process in intrinsic or nonallergic asthma, studies so far indicate that histologically there is no difference between intrinsic and extrinsic asthma. Occupational asthma, which cannot always be attributed to an IgE mediated mechanism, also shows similarities to extrinsic asthma.

Epidemiology

Australian studies indicate that the prevalence of reported wheeze is up to 20%. Serial Australian studies uniformly show increases in wheeze and diagnosed asthma, the latter increasing from 9% to 16% between 1981 and 1990 [55][56]. Over the same period the level of atopy has remained the same. Although a change in diagnostic patterns could be responsible for this increase, the rise in objectively measured AHR and similar increases in asthma noted in other countries suggests that a real increase has occurred. Supporting this, in a study of children and parents with the same environment and dust mite sensitivity the children had a higher prevalence and severity of AHR and asthma [57]. Significant genetic changes are unlikely to occur over one generation, possible environmental changes which would predispose to increased allergic disease are increased allergen exposure and maternal smoking. In general there is a higher incidence of asthma in developed countries.

Natural History and Progression of Asthma

Over half of the children who wheeze in early childhood will become symptom free by early adulthood. Predictors of persisting asthma include more severe disease and atopy. Prospective studies show that a large proportion of these have asymptomatic AHR and about 30% will experience symptom recurrence.[58]. In adulthood there is a small incidence of remission of about 1% per annum, again most likely to occur in milder asthmatics[59].

A variety of clinical patterns of asthma can be described and are listed in Table 1. Other important clinical subgroups include the triad of asthma, nasal polyposis and aspirin sensitivity, asthma associated with irreversible airflow limitation and occupational asthma including reactive airway dysfunction syndrome.

Asthma deaths have shown a gradual increase since World War 11, with significant peaks in the 1960s and 1980 - 1990s. Current death rates vary between countries but are approximately 1 per 100,000 in 5-34 year olds. In Australia death rates have been approximately 600 per year over the last few years but in the last twelve months have significantly

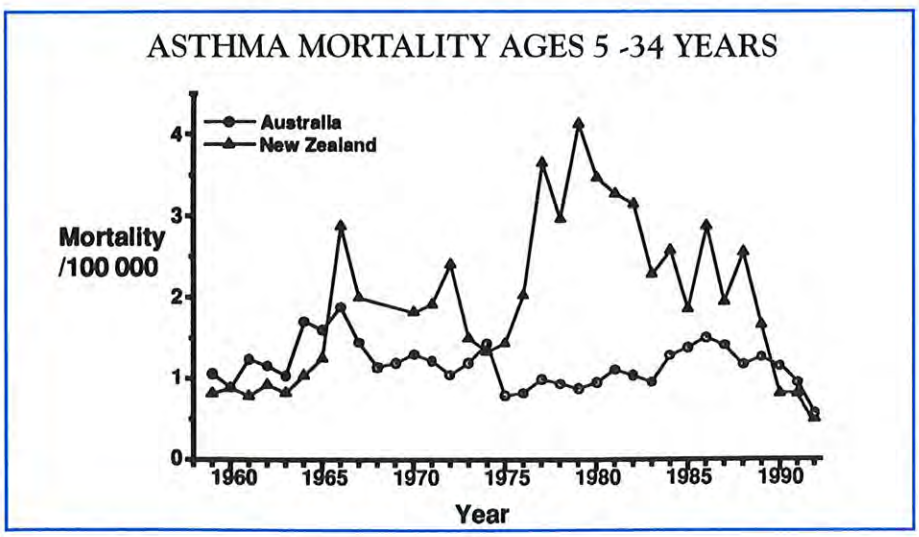

Figure 4. Asthma mortality per 100,000 population in Australia and New Zealand between the years 1955 and 1992

fallen (Figure 4). Although not possible to prove it is widely felt that the most plausible explanation for the increased mortality in the 1960s was the use of non-selective B-agonist inhalers.[60] More recent rises in asthma mortality have been documented in Australia and New Zealand, with case control studies suggesting that poor asthma control and/or undertreatment were contributing factors [61]. Data from Saschatchewan, US where computer records of all prescriptions are available, implicate excess use of B agonists especially the use of greater than 2 cannisters of inhaled B agonist per month as a high risk factor for asthma death [62]. In all these studies it is difficult to distinguish between cause and effect, in other words whether excess B-agonist use predisposes to asthma death or whether it is merely a marker of severe poorly controlled asthma.

The B-agonist debate in asthma remains unresolved but has led to a more cautious use of these agents. These agents are used for symptom control but several studies suggest that regular use of B2 agonists make asthma worse either with increased symptoms, AHR or a decline in lung function [63]. Overall these findings have led to a more frequent use of inhaled corticosteroids and switching from regular to "as necessary" use of B-agonists

Clinical Management of Asthma

A combination of clinical history and lung function testing allows assessment of the severity of asthma. Poorly controlled asthma is characterised by frequent symptoms, nocturnal asthma, abnormal lung function and in severe cases recurrent hospital admissions.

Lung function assessment should include measurement of FEV1, PFR if these are normal a flow volume curve, and response to a bronchodilator should also be undertaken. Histamine bronchoprovocation is useful to exclude a diagnosis of current asthma and to assess the severity of asthma particularly if a discrepancy between perceived symptoms and disease severity is suspected. It is appropriate for the majority of asthmatics on regular treatment to keep peak flow diaries - these are used to assess diurnal variability of PFR which has been shown to reflect asthma severity and also to teach asthmatics how to self-medicate during an exacerbation of their asthma.

Trigger Factors in Asthma

- Allergens
- Cough
- Drugs (Aspirin, NSaids, Beta Blockers)
- Exercise (Cold Dry Air)
- Food Additives (Metabisulphite, MSG, Tartrazine)
- Gastroeosophaegal Reflux
- Laughter
- Obstructive sleep apnoea
- Pollutants
- Rhinitis
- Smells
- Stress
- Tobacco Smoke

Table 3.

Aims of treatment include control of symptoms, normalisation of lung function and reversal of bronchial hyperresponsiveness.

Current treatment depends on the use of bronchodilators such as B-agonists, anticholinergics, theophyllines and prophylactic agents such as inhaled corticosteroids and sodium cromoglycate. There has been a significant trend towards the use of prophylactic agents, as these have been shown to reduce bronchial inflammation. Over the last 10 years much larger doses of inhaled corticosteroids have been used, increasing from a standard dose of 800Ug to 1600Ug and often more in difficult asthma. At doses over 600-800Ug in children and 1600Ug in adults systemic side effects can be detected. New drugs include a 12 hour B-agonist called salmeterol which is ideal to treat nocturnal asthma, newer topical corticosteroids such as budesonide and now fluticasone proprionate. Other preparations include antiallergic drugs ketotifen and nedocromil both used overseas but not available in Australia. A new nonsedating antihistamine cetirizine may be relevant for its anti-eosinophil effect, but is still being evaluated.

Much progress has been made in different types of inhaler devices, partly attributable to the planned phasing out of CFCs, with the introduction of a dry powder inhaler device, the turbohaler. Other devices include spacing chambers, autohalers and nebulisers. Numerous data show that up to 30% of patients use aerosol inhalers incorrectly; however, it should now be possible to choose an inhaler device that will suit any patient.

Trigger factors are numerous (Table 3), and some of these have been discussed above, and should be thoroughly assessed so that avoidance measures, if available, can be instituted.

Education has played an increasingly important role in the management of asthma, both education of the patient by the treating doctor and the use of widely available workshops. The National Asthma Campaign launched in 1990 has been a significant cooperative approach to try and improve the treatment of asthma in Australia with recent falls in asthma mortality suggesting that it has been successful.

References

1. National Asthma Campaign NAC Report of the cost of asthma in Australia 1993
2. National Heart, Lung and Blood Institute National Asthma Education Program Expert Panel Report. Guidelines for the diagnosis and management of asthma. Paed. Asthma All. Immunol. 1991;5:57.
3. Kendrick AH, Higgs CMB, Whitfield MJ, Laszlo G. Accuracy of perception of asthma: patients treated in general practice. BMJ 1993;307:422-4.
4. Hargreave FE, Ryan G, Thomson NC et al. Bronchial responsiveness to histamine or methacholine in asthma: measurement and clinical significance. J All & Clin Immunol. 1981:68;347-355.
5. Manresa Presas F, Romero Colomer P, Rodriguez Sanchon B. Bronchial hyperreactivity in fresh stage 1 sarcoidosis. Ann NY Acad Sci. 1986;465:523-529.
6. Pang J, Chan HS, Sung JY Prevalence of asthma, atopy and bronchial hyperactivity in bronchiectasis: a controlled study. Thorax 1989;44:948-951.
7. Banner NR, Heaton R, Hollingshead L, Guz A, Yacoub MH. Bronchial reactivity after combined heart lung transplantation. Thorax 1988;48:955-959.
8. Peat JK, Haby M, Spijker J, Berry G, Woolcock AJ. Prevalence of asthma in adults in Busselton, Western Australia. BMJ,1992:305:1326-1329.

9. Pattemore PK, Asher MI, Harrison AC. The interrelationship among bronchial hyperresponsiveness, the diagnosis of asthma, and asthma symptoms. Am Rev Resp. Dis. 1990;142:549-554.
10. Clifford RD, Howell JB, Radford M, Holgate ST Associations between respiratory symptoms, bronchial response to methacholine, and atopy in two age groups of schoolchildren. Arch. Dis. Childh. 1989;64:1133-9.
11. Roche WR, Beasley R, Williams JH et al. Subepithelial fibrosis in the bronchi of asthmatics. Lancet 1989;1:520-524.
12. Brewster CEP, Howarth PH, Djukanovic R, Wilson J, Holgate ST. Myofibroblasts and subepithelial fibrosis in bronchial asthma. Am J Respir Cell Mol Biol 1990;3:507-511.
13. Menglers HJ, Maikoe T, Brinkman L, Hooibrink B, Lammers JJ, Koenderman L. Immunophenotyping of eosinophils recovered from blood and BAL of Allergic Asthmatics. Am J Respir Crit Care Med 1994;149:345-351.
14. Montefort S, Roberts JA, Beasley R, Holgate ST, Roche WR. The site of disruption of the bronchial epithelium in asthmatic and nonasthmatic subjects. Thorax 1992;47:499-503.
15. Elwood RK, Kennedy s, Belzberg A. Respiratory mucosal permeability in asthma. Am Rev. Resp. Dis. 1983;128:523.
16. Flavahan NA, Aarhus LL, Rimele TJ, Vanhouette PM. Respiratory epithelium inhibits bronchial smooth muscle tone. J Appl. Physiol. 1985;:58:834.
17. Ricci M, Rossi O, Bertoni M, Matucci A. The importance of Th2-like cells in the pathogenesis of airway allergic inflammation. Clin Exptl Allergy 1993,23:360-369.
18. Bradley BL, Azzawi M, Jacobson M et al. Eosinophils, T lymphocytes, mast cells, neutrophils and macrophages in bronchial biopsy specimens from atopic subjects without asthma and normal control subjects and relationship to bronchial hyperresponsiveness. J. All. Clin. Immunol. 1991;88:661-74.
19. Rimmer SJ. Histamine releasability in asthma. MD Thesis. UNSW 1986.
20. Sedgewick JD, Holt PG, Turner KJ. Production of a histamine releasing lymphokine by antigen or mitogen stimulated human peripheral T cells. Clin. Exp. Immunol 1981;45:409-418.
21. Spry CJF. Eosinophils. New York:Oxford Univ. Press 1988:272.
22. Clelland CA, Higgenbottam TW, Stewart S, Scott JP, Wallwork T The histological changes in transbronchial biopsy after treatment of acute lung rejection in heart-lung transplants. J Pathol 1990;161: 105-112.
23. Gibson PG, Denburg J, Dolovich J, Ramsdale EH, Hargreave FE. Chronic cough:eosinophilic bronchitis without asthma. Lancet 1989;i:1346-8.
24. Boulet LP, Milot J, Boutet M, St Georges F, Laviolette. Airway Inflammation in nonasthmatic subjects with chronic cough. Am J Respir Crit Care Med 1994;149: 482-489.
25. Carney I, Gibson PG, Borgas T, Hopkins YK Upper airway responsiveness and airway inflammation in chronic cough. TSANZ Proceedings 1994;P45.
26. Gibson PG, Wlodarczyk J, Hensley MJ, Gleeson M, Henry M, Cripps AW, Clancy R. Airway inflammation and asthma symptoms in a birth cohort .TSANZ 1994:P70.
27. Power C, Sreenan S, Hurson B, Burke C, Poulter LW. Distribution of immunocompetent cells in the bronchial wall of clinically healthy subjects showing bronchial hyperresponsiveness. Thorax 1993;48:1125-1129.
28. Rimmer J, Anson D, Trevallion L, Woolcock AJ. Assessment of cellular activation in the peripheral blood of asthmatics. TSANZ 1994: P39.
29. Zimmerman B. Clinical experience with the management of ECP: usefulness in the management of children with asthma. Clin & Exp Allergy 1993,23,suppl 2: 8-12.
30. Hogg JC, James AL, Pare PD. Evidence for inflammation in asthma. Am. Rev Resp Dis 1991;143:S39-42.
31. Amour CL, Reade MC, McReade, Caughey GH, Black JL. Evidence for an increased responsiveness to histamine in human sensitised bronchus. TSANZ 1994:P153.
32. Barnes PJ. Neural control of human airways in health and disease. State of the Art. Am. Rev. Resp. Dis. 1986;134:1289-1314.
33. Cookson WOCM, Sharp PA, Faux JA, Hopkin JM, Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. Lancet 1989;(i):1292-1295.
34. Duffy M.personal communication.
35. Leung R, Burdon J, Carlin J, Czarny D. Risk factors for asthma and allergy in Asian immigrants in Melbourne. TSANZ 1994: P64.
36. Burney PGJ Evidence for an increase in atopic disease and possible causes. Clin Exptl Allergy 1993;23:484-492.
37. Post-natal tobacco smoke exposure predisposes to respiratory infections and the development of allergic disease. Wittig Jh, McLaughlin ET, Leifer KL, Belloit JD. Risk factors for the development of allergic disease: analysis of 2190 patient records. Ann Allewrgy 1978;41:84).
38. Ishizaki T, Koizumi K, Ikemori R, Ishiyama Y, Kushibiki E. Studies of prevalence of Japanese cedar pollenosis among the residents in a densely cultivated area. Ann Allergy 1987;58:265-270.
39. Magnussen H, Jorres R, Nowak D. Effect of air pollution on the prevalence of asthma and allergy: lessons from the German reunification. Thorax;1993:879-881.
40. Burney PGJ, Neild JE, Twort CHC et al. The effect of changing dietary sodium on the bronchial response to histamine. Thorax 1989;44:36.
41. Anto JM, Sunyer J, Roderigez RL et al Community outbreaks of asthma associated with inhalation of soybean dust. New Eng. J. Med. 1989;320:1097.
42. Packe GE, Ayres JG. Asthma outbreak during a thunderstorm. Lancet 1985; ii:199-204.
43. Corbett S, Hensley M, Gibson P, Bek M, Katelaris C. Epidemic asthma in Tamworth. A report to the Chief health Officer. 1991. NSW Dept Health Publication.
44. Empey DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA. Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infections. Am. Rev. Resp. Dis. 1976;113:131.
45. Pullan Cr, Hey EN. Wheezing, asthma and pulmonary dysfunction 10 years after infection with RSV in infancy. Brit. Med. J. 1982;284:1665-1669.
46. Lau S et al High mite allergen exposure increases the risk of sensitisation in atopic children and young adults. J.All. Clin.Immunol. 1989;84:718-26.
47. Platts Mills TAE & de Weck AL Dust mite allergen and asthma - a world wide problem. J.All.Clin.Immunol. 1989; 83:416-27.
48. Peat JK and Woolcock AJ Sensitivity to common allergens: relation to respiratory symptoms and bronchial hyperresponsiveness in children from three different climatic areas of Australia. Clin Exp Allergy 1991;21:573-81.
49. Gelber LE et al. Sensitisation and exposure to indoor allergens as risk factors for asthma among patients presenting to hospital. Am. Rev. Resp. Dis. 1993;147:573-8.
50. Sporik R , Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house dust mite allergen (Der p1) and the development of asthma in childhood - a prospective study. New Eng.J.Med. 1990;323:502-507.
51. Knox RB. Grass pollen, thunderstorms and asthma. Clin Exptal Allergy, 1993;23:354-359.
52. King CM, Thompson PJ, Stewart GA. Responses of airway epithelium to proteolytic dust mite allergens. TSANZ 1994:P159.
53. Herbert CA,Holgate ST, Robinson C,Thompson PJ, Stewart GA. Effect of mite allergen on permeability of bronchial mucosa. Lancet 1990;ii:1132.
54. O'Keefe PT, Young S, Arnott J, Henderson J, Stewart GA, LeSouef PN, Landau LI. Der p1 exposure and increased airway responsiveness in early infancy. TSANZ Proceedings 1994.
55. Peat JK et al Prevalence of Asthma in adults in Busselton, Western Australia BMJ, 1992;305:1326-9.
56. Robertson CF et al Prevalence of asthma in Melbourne schoolchildren: change over 26 years. BMJ 1991;302:1116-8.
57. Peat JK, Mellis CM, Leeder SR, Woolcock AJ. Severity of asthma in children and their parents. TSANZ Proceedings 1993:P54.
58. Kelly WJW, Hudson I, Phelan PD, Pain MCF, Olinsky A. Childhood asthma in adult life: a further study at 28 years of age. Br. Med J. 1987;294:1059-1062.
59. Bronnimann S, Burrows B. A prospective study of the natural history of asthma: remission and relapse rates. Chest 1986;90:480-484.
60. Inman WHW and Adelstein AM. Rise and fall of asthma mortality in England and Wales in relation to the use of pressurised aerosols. Lancet 1969;ii:279.
61. Rea HH, Sears MR, Beaglehole R et al. Lessons from the national asthma mortality study: circumstances surrounding death. NZ Med J. 1987;100:10.
62. Suissa S, Ernst P, Boivin J-F, Horwitz R.I. et al A cohort analysis of excess mortality in asthma and the use of inhaled B-agonists. Am J Rep Crit Care Med 1994;149:604-10.
63. Sears MR, Taylor RD, Print CG et al. Regular inhaled B-agonist treatment in bronchial asthma. Lancet 1990;336: 1391-1396.

Dr Paul J Kelly

Osteoporosis: Recent Advances in Prevention and Therapy

Introduction

Osteoporosis is an increasingly major health problem in Western societies. With the "ageing" of these societies, the prevalence and impact of this condition, in terms of morbidity and mortality, as well as financial cost to the community will increase. A number of recent advances will be reviewed which have provided useful strategies for the prevention and treatment of osteoporosis and insights into the pathogenesis of this common and crippling condition. In this review particular attention will be directed towards advances in our understanding of the impact of osteoporosis, methods of prevention and the impact of calcium intake, and recent inroads into our understanding of the genetics of osteoporosis.

Osteoporosis Epidemiology

Osteoporosis can generally be regarded as a reduction in bone density that leads to an increased risk of fracture. Data in the past regarding the impact of osteoporosis has centered largely on hip, forearm and vertebral fractures. Recent data from a unique Australian study, the Dubbo Osteoporosis Epidemiology Study (DOES), indicates that as many as 60% of Australian women and 30% of men in the over 60 year age-group can expect an osteoporotic fracture in their lifetime (Jones et al 1994a). Also data from this study indicates that the total cost to the Australian community is around $A700 million per annum (Randal, manuscript in preparation).

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Epidemiological studies have now clearly established that bone density predicts fracture (Nguyen et al 1993, Cummings et al 1993). There is an logarithmic relationship between bone density and bone strength in vitro such that small changes in bone density result in proportionately larger changes in bone strength. This observation can be translated into the clinical environment. For example, at any age an individual with a hip bone density one standard deviation below mean has at least a doubling of risk of fracture at that site (Cummings et al 1993). Data from DOES also demonstrates that fractures in the elderly are predicted by a model that includes bone density, quadriceps muscle strength, and postural stability, with the bulk of the prediction arising from bone density (Nguyen et al 1993). Interestingly, this observation holds for all osteoporotic fractures in both men and women and probably reflects the interaction between bone strength and risk of falling. Postural stability predicts falls in the elderly and factors that contribute to body sway in this group need to be identified. In this regard a number of studies are underway assessing the role of exercise in the prevention of falls in the elderly.

With regard to bone density changes in the elderly, based on cross-sectional bone density measurements it has been assumed and become part of dogma that bone density changes were slight in the those over the age of 60. Recent data now indicates that, at least at the proximal femur, the rate of bone loss in the elderly is around 1% per annum and bone loss tends to accelerate with advancing age with rates of loss of up to 4% per annum in those over the age of 80 (Jones et al 1994b). Interestingly this accelerated bone loss occurs in both men and women. Similar changes were not observed at the lumbar spine where osteoarthritis and degenerative changes can interfere with the precision of serial bone density measurements. The observation of rapid bone loss in the elderly suggests that attention to osteoporosis prevention should extend to all age groups, not just the young or perimenopausal women and that the over 80's may be a high risk group to be targetted for intervention. Identifying the factors that determine this loss of bone will be important to isolate strategies that may be useful in the further prevention of osteoporosis in the elderly.

Risk factors for osteoporosis

Osteoporosis may be a manifestation of a number of conditions (Table 1). Osteoporosis is a heterogeneous disorder which has multiple contributing factors, both genetic and environmental. There are several "risk factors" including low dietary calcium intake, poor level of physical activity, low body weight, tobacco consumption and caucasian race. However these factors are not adequate to discriminate between those with low and normal bone density. Therefore such risk factors analysis is rarely useful clinically to identify risk of osteoporosis, which can only be ascertained at present by bone densitometry.

While alcohol intake probably adversely affects bone density only when consummed in excess, tobacco consumption at all levels tends to be associated with lower bone density. A recent twin study revealed that one twin who smoked had lower bone density than their non-smoking co-twin and that 20 years of consumption of 20 cigarettes per day was associated with around 10% lower bone density or roughly a doubling of fracture risk (Hopper and Seeman, 1994).

Prevention of osteoporosis

Bone density in adults is the cumulative result of both peak bone mass achieved in early adulthood and the amount of decline that has occurred since that time. Thus prevention of osteoporosis can be focused on maximising peak bone density and / or preventing age and postmenopausal bone loss.

Causes of osteoporosis.

1. Osteoporosis unassociated with systemic disease:

Postmenopausal Osteoporosis

"Idiopathic" Osteoporosis

2. Osteoporosis associated with systemic disease:

Endocrine disorders

eg; hypogonadism, hyperthyroidism, hyperparathyroidism, Cushing's disease

Chronic renal and liver disease

Malabsorption

Multiple Myeloma

Mastocytosis

3. Heritable disorders of connective tissue:

eg; Osteogenesis Imperfecta, Marfan's syndrome or Ehlers-Danlos syndrome

4. Drug induced

Corticosteroids

Alcohol (at excessive levels)

Heparin treatment (long term)

Thyroxine suppressive therapy

Table 1.

Bone density in the elderly is contributed equally by peak bone density and age and postmenopausal bone loss. Factors that interfere with the development of peak bone mass may therefore also contibute to future risk of osteoporosis. Eating disorders can contribute a number of problems including weight loss, hypogonadism and dietary calcium deficiency. Similarly exercise induced hypogonadism may prevent the attainment of skeletal mass that occurs rapidly throught puberty. The length of time of amenorrhoea, and hence hypogonadism, has been shown to be directly related to the loss of bone density in women with eating disorders. Studies are presently being undertaken to ascertain if the use of oestrogen replacement in the form of the oral contraceptive pill can lessen the risk of bone density loss and failure to obtain peak bone density (Seeman et al 1992). In young women with eating disorders or exercise induced oligoamenorrhoea some form of oestrogen replacement is probably worthwhile.

Oestrogen Replacement

Long term oestrogen replacement remains the mainstay of osteoporosis prevention. Long term therapy, at least 5 years or more, can prevent up to 50% of hip and 90% of spinal fractures. Oestrogens prevent bone loss through interaction with oestrogen receptors on osteoblasts thereby affecting the synthesis and release of other mediators of bone resorption.

Oestrogen therapy appears to be effective in patients at least up to 75 years of age. However, to obtain maximum advantage from this therapy, it should begin as soon as possible after the menopause and continued for at least 20 years if not life long (Felson et al 1993). The beneficial effects can be achieved by any route of administration, including vaginal, subcutaneous implant or transdermal. The minimal effective dose has not clearly been established, although for conjugated equine oestrogen the oral dose appears to be 0.625 mg/day, 1.25 mg piperazine oestrone sulphate, and 4mg transdermal oestradiol twice weekly. Some data suggest that lower doses of oestrogen can be used in combination with either continuous progesterone or calcium although further work in this area is required. Oestrogen replacement will prevent bone loss in the majority of women, however, up to 20-30% of postmenopausal women may still lose bone on oestrogen replacement. Tobacco consumption may increase the conversion of oestrogens to less active metabolites, and may be a factor in some women who require higher doses of oestrogen to prevent bone loss.

Not all postmenopausal women require oestrogen replacement. In women concerned regarding their risk of osteoporosis, and in whom the administration of oestrogen will be determined by this, bone densitometry may be useful. The decision to commence oestrogen replacement is often made on other grounds, for example the presence of menopausal symptoms. Estimation of future fracture risk may be useful in a woman who is unsure whether to continue long term oestrogen or to cease therapy after oestrogen deficiency symptoms are likely to have abated. Unfortunately, long term compliance with oestrogen replacement is poor and as many as 50% of women may have discontinued their treatment within 6 months.

In those women with prior histories of breast cancer who require osteoporosis prevention, the synthetic anti-oestrogen, tamoxifen, which has mild oestrogen like effects on bone, liver and genital tissue in women, may be a useful strategy. A number of studies have now indicated that tamoxifen 20 mg daily can prevent postmenopausal bone loss at both the lumbar spine and femoral neck (Ward et al 1993). There may be an increase in risk of endometrial carcinoma with long term tamoxifen therapy and concurrent progesterone has been advocated to reduce this risk. Raloxifene, a partial oestrogen agonist with apparent oestrogen-like effects on bone, but with little effect on the endometrium (Black et al 1994), is currently undergoing clinical studies in osteoporosis prevention.

Other alternatives to oestrogen replacement are being investigated. Bisphosphonates are potent inhibitors of bone resorption. Tiludronate and alendronate, newer agents in this category, may be effective in the prevention of postmenopausal bone loss. These agents at present are to be viewed as investigational and are not available in Australia as yet for the prevention of osteoporosis.

Physical Activity

Bone density is higher in those individuals with moderate levels of physical activity and hence greater muscle strength and extremes of physical activity have definite affects on bone mass. However whether changing the level of exercise in the ambulant non-athletic population affects bone density in the long term remains unclear and clinical results have been disappointing. The optimal frequency and intensity of physical activity required to alter bone density still needs to be established. There is a lack of well controlled clinical studies to address the effect of exercise training on bone density in adults, and at best a 1-2% effect on bone density may observed after up to 12 months of training for up to 4-6 hours per week. Moreover the bone gained may be lost on de-training. Furthermore compliance with long term (>12 months) community exercise programmes is usually poor and strategies to improve long term compliance are required before embracing exercise to augment bone density. There is little evidence that exercise alone can stop postmenopausal bone loss but may slow bone loss at this time when combined with calcium supplementation. However, evidence is accumulating that physical activity, at modest levels may have positive influences on the attainment of peak bone mass. In some women this benefit may be offset by exercise induced hypogonadism.

A major effect of exercise may be to improve postural stability in the elderly. Exercise may have a role however in the maintenance of postural stability and prevention of falls, thereby preventing osteoporotic fracture. This however remains to be demonstrated in clinical studies.

Calcium Intake

Recent studies support a role for dietary calcium in the attainment of peak bone density. In a recent study, a significant benefit on bone density of calcium supplementation of 1000 mg in children was observed (Johnston et al 1992). Interestingly, this benefit occurred in prepubertal but not pubertal children. It is possible that, at puberty, the effect of sex hormones on skeletal

development may be so marked as to mask even moderate effect of calcium intake. Others have observed an influence of calcium supplementation on the rate of increase in pubertal girls. Lloyd et al (1993) found that calcium supplmentation (500mg calcium citrate malate daily) to a group of girls aged 12 years, resulted in increases in total body and spine density over changes observed in girls receiving placebo. This change in calcium intake represented an increase from 80% of recommended daily intake to 110% and the effect translates into an additional 1.3% increase in skeletal mass during pubertal growth. These data then support a role for calcium intake in the attainment of peak bone mass. Similar studies are underway to the role of calcium intake in Australian adolescents.

Calcium intake cannot be viewed in isolation from other lifestyle factors that may affect bone mass. There is evidence of an effect of calcium intake, interacting with physical activity, on bone density in young women, with those women with the highest calcium intake and exercise levels having the greater bone density (Recker et al 1992).

With regard to postmenopausal bone loss, dietary calcium supplementation may slow bone loss, by around 40%, in women more than 3 years since menopause but is not an alternative to oestrogen replacement in the prevention of osteoporosis (Reid et al 1993).

Corticosteroid Induced Bone Loss

Osteoporosis is a major complication of corticosteroid therapy. Corticosteroids induce osteoporosis by various mechanisms. Impaired intestinal calcium absorption may give rise to mild secondary hyperparathyroidism with enhanced bone resorption. Also suppression of bone formation can occur with corticosteroid therapy. These effects on bone metabolism can be complicated also by hypogonadism which may occur in response to corticosteroid effects on the hypothalamic-pituitary gonadal axis. Whether a "safe" dose of corticosteroids exists is still debated with some studies suggesting that doses equivalent to less then 10mg prednisolone per day do not cause bone loss where as others indicate alteration in bone metabolism with doses between 5-10mg prednisolone daily. Also alternate day therapy does not offer any protection from bone loss.

Approaches to the Management of Corticosteroid Induced Osteoporosis

- measure bone density prior to or shortly after the commencement of corticosteroids
- monitor bone density changes within the first 6-12 months of therapy
- minimise corticosteroid dose where possible
- consider;
  - oestrogen replacement in postmenopausal women
  - testosterone in men with low testosterone levels
- calcitriol to prevent spinal bone loss in those commencing corticosteroids
- bisphosphonates should be considered in those with established steroid induced osteoporosis

Table 2.

As with other forms of osteoporosis, prevention probably holds the best prospect of altering the impact of corticosteroid induced osteoporosis (Table 2). Importantly, bone loss associated with osteoporosis with corticosteroid excess is reversible, at least in part, and withdrawal or minimisation of corticosteroid dose should always be considered (Pocock et al 1987, Hall et al 1993). However this is often not possible and strategies to prevent bone loss at the onset of corticosteroid therapy need to be identified.

Prevention of corticosteroid induced bone loss

Recent work indicates that calcitriol, the active form of vitamin D, (mean dose 0.60 microg daily), and /or nasal calcitonin when combined with calcium can prevent bone loss at the lumbar spine in the first 12 months after commmencing corticosteroids therapy (Sambrook et al 1993). However bone loss at the proximal femur was not prevented with this regimen. Other studies support a role for the bisphosphonates with some evidence to support the use of bisphosphonates (Reid et al 1988). In postmenopausal women, the effects of oestrogen deficiency may potentiate the adverse effects of corticosteroids on bone consideration should always be given to oestrogen replacement.

Interventions then have been identified that can at least in part prevent bone loss with corticosteroids. It behoves those who prescribe corticosteroids to consider osteoporosis prevention in those commencing such therapy especially when given at moderate to high dose in elderly men or postmenopausal women. Bone densitometry prior to or shortly after commencing corticosteroids is the only reliable method of identifying those at risk of developing osteoporosis with corticosteroid therapy

Bone loss following organ transplantation

Transplantation is becoming more widely used in the treatment of chronic organ failure with much success. With the improved survival of patients receiving transplants, attention has been drawn to some of the long term complications of therapy that prevent rejection of the donor organ. Osteoporosis is common following transplantation with an incidence of vertebral fracture of up to 30% and relates not only to corticosteroid therapy (Katz and Epstein, 1992). Cyclosporin A results in a form of high bone turnover with osteoporosis in rats and similar findings have been observed in humans (Katz et al 1994). Also physical inactivity and effects of illness and high dose corticosteroids on sex hormone levels may also play a role. Bone loss following cardiac and / or lung transplantation is rapid with up to 6-10% loss of vertebral density within the first 6 months following transplantation (Sambrook et al 1994). Because of the

effects of cycloporin A on bone it is difficult to transfer the findings of studies on the prevention of corticostreoid induced bone loss to the setting following organ transplantation. However, studies are in progress to assess the role of calcitriol and calcium in the prevention of post-transplantation bone loss and hopefully rational preventative strategies will be devised in the near future.

Treatment of Established Corticosteroid Induced Osteoporosis

Our understanding of corticosteroid induced bone loss has been confounded by a lack of well designed longitudinal studies and the difficulty in controlling for the effect of the underlying disease requiring corticosteroid therapy. However from the data to date, bone loss with corticosteroid therapy appears to be most rapid within the first 6-12 months of therapy and then may plateau despite ongoing use of corticosteroids. Therefore the appoach to the patient who has osteoporosis identified after receiving corticosteroids for many years may differ from the approach used to prevent bone loss after initiation of corticosteroids. Bisphosphonates may be effective in increasing bone density in this setting (Reid et al 1988) while the role of calcitriol in this setting is not established. An approach supported by current data would be the use of cyclical etidronate possibly combined with oestrogen replacement in postmenopausal women.

Genetic Influences on Osteoporosis Risk

A large proportion of the population variance in bone density and therefore osteoporosis risk relates to genetic influences. Interestingly twin and family studies suggest the bulk of this genetic effect may lie in the attainment of peak bone density, although genetic factors may also affect the rates at which bone density changes after attainment of peak bone mass. Understanding the genetic factors that may affect bone density offers a promise of insight into the pathogenesis of osteoporosis and perhaps, in the long term, better therapies.

Twin Studies of Bone Turnover

Bone is continually renewing itself and in the adult skeleton under normal circumstances new bone laid down by osteoblasts exactly matches osteoclastic bone resorption, i.e. formation and resorption are closely 'coupled'. Biochemical markers of bone turnover, which are non-invasive estimates of the relative influences of bone formation and resorption, have allowed study of the genetic regulation of bone metabolism.

Certain biochemical parameters and markers of bone turnover appear to be under strong genetic control (Kelly et al 1993, Tokita et al 1994). Recent studies in twins suggest strong genetic effects on osteoblast function and bone turnover generally. Thus in adult twins the majority of the population variance in serum osteocalcin, an osteoblast product, was determined by genetic factors (Kelly et al 1994). Importantly, in non-identical twins, where within twin-pair differences in serum osteocalcin levels may reflect genetic variance, differences in osteocalcin predicted within-pair differences in bone density at both the lumbar spine and femoral neck, with twins with the higher osteocalcin value being associated with the lower bone density. Overall these data provide additional support for the hypothesis that the genetic influence on bone density is mediated through genetic regulation of bone modelling.

Mechanisms of Genetics Effects on Bone Density

Vitamin D Receptor Gene

Vitamin D has a central role in regulation of bone and calcium homeostasis, regulating a network of genes in various tissues and cell types. The target genes for 1,25 dihydroxyvitamin D action include key regulatory and structural genes in all the major sites of calcium homeostasis including bone, gut, kidney and parathyroid glands. Moreover, since osteocalcin production and collagen synthesis are regulated by the active hormonal form of vitamin D, 1,25 dihydroxyvitamin D, genetic pathways involving vitamin D seemed likely candidates for the genetic effects on bone. 1,25

Dihydroxyvitamin D acts on the osteocalcin gene via the vitamin D receptor (VDR). It has the capacity to act as a potent amplifier of gene regulatory signals. The amplification process means that modest differences in the expression of the VDR could be expressed in large differences in the end product or the expression of a target gene.

Recently common allelic variation in the VDR gene has been identified by restriction fragment length polymorphism analysis and shown to predict serum osteocalcin in normal women (Morrison et al 1992). Due to inherent difficulties identifying multiple generation family studies for the assessment of linkage in osteoporosis, dizygotic twins have been used as a form of sib-pair analysis to expore linkage between these VDR gene alleles and bone density. In such analysis linkage between VDR gene alleles and the bone density phenotype has been supported (Morrison et al 1994) (Figure 1). Dizygotic twins with the same VDR genotype had bone densities almost as similar as those of monozygotic twins, while those with different VDR allelotypes differed by up to 20% in bone density at spine and hip sites. Moreover twins with the low bone density allele had lower bone density than their co-twin. The same effect on bone density was observed in an unrelated normal population sample (Morrison et al 1994). These data suggest that one particular VDR gene allele appears to determine higher bone turnover and lower bone density in both twin and unrelated populations. This model of assessment of the relationship between potential gene markers and bone density, by using DZ twins as sib pairs will be useful in the assessment of other candidate genes that no doubt contribute to the genetic variation in bone density.

More recent data also support an a relationship between VDR gene alleles and fracture. In the Dubbo Osteoporosis Epidemiology Study a significant association between genotype and fracture incidence in the elderly has been observed (White et al 1994) with

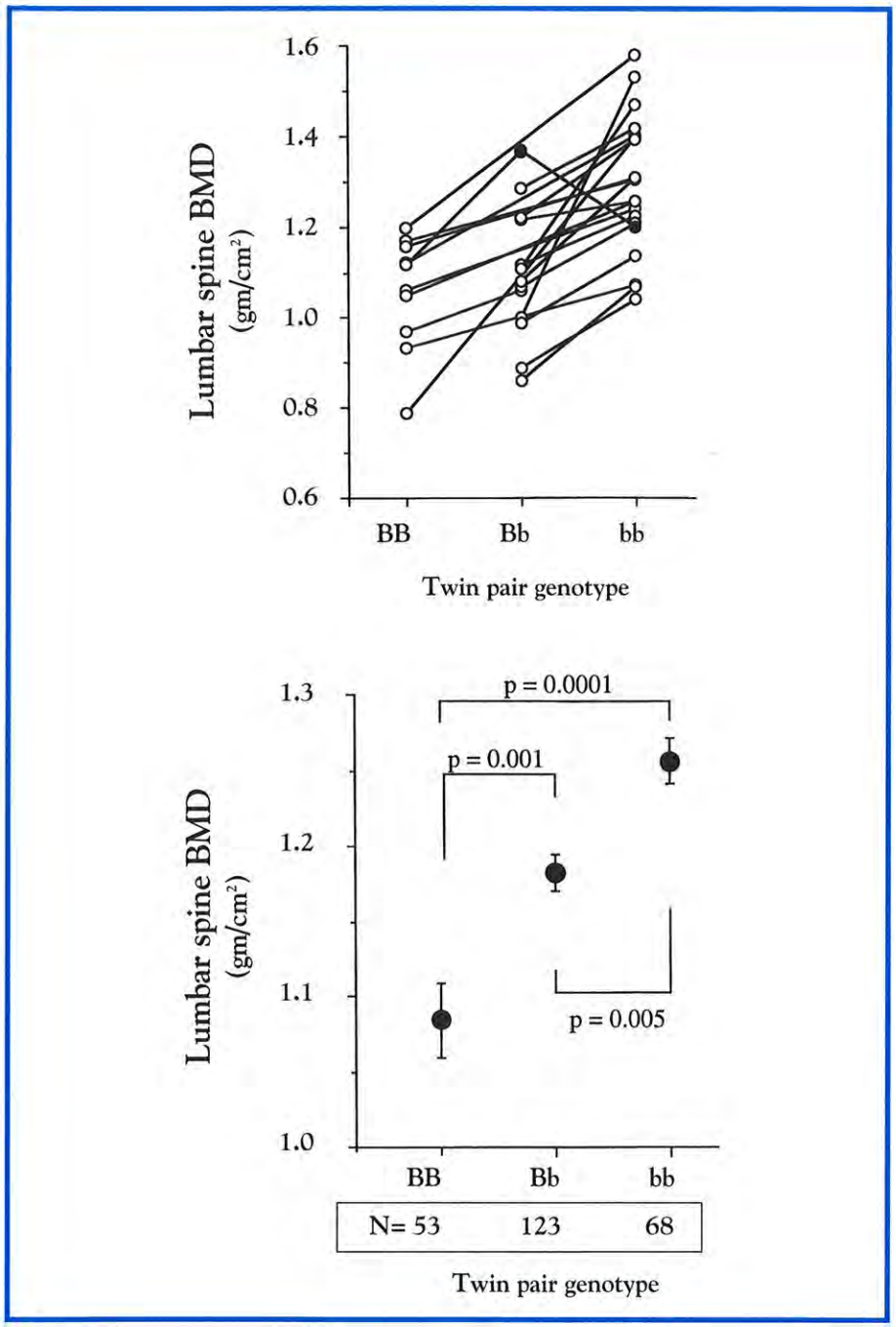

Figure 1. The relationship between bone density and vitamin D receptor gene alleles in twins. The top panel describes the lumbar spine density in 22 pairs of non-identical twins plotted as twin vs co-twin, with the lines joining the twin pairs. Note in 21 of the 22 pairs the twin with the B allele has the lower bone density. The bottom panel describes the lumbar spine bone density in all twins regardless of zygosity. Note again that the B allele is associated with lower bone density. (copyright Nature, reproduced with permission)

the "low bone density" allele associated with more than doubling of fracture risk. Further large scale studies are now underway to study the relationship between fracture rate and VDR gene alleles.

Since the VDR allele effects on bone density correlate with osteocalcin level differences and the osteocalcin and VDR genes are encoded on different chromosomes, the most likely mechanism of these effects is through a functionally different VDR, either in quantity or activity. Although it is possible that the VDR alleles are merely in linkage disequilibrium with the effect gene, this seems unlikely given the centrality of the vitamin D endocrine system to bone and calcium homeostasis and preliminary data indicating differences in the vitamin D endocrine system between individuals with the different VDR genotype (Howard et al, manuscript submitted). Preliminary data suggest that normal women with differing VDR gene alleles respond differently to short term calcitriol. The challenge remains however to clarify the physiological correlates of the VDR gene alleles and the molecular mechanisms underlying the affect on bone metabolism. The amplifying nature of transacting factors makes it possible that the relatively large differences observed in bone density, osteocalcin and other bone turnover marker levels could be due to very subtle differences in receptor level or function. The two major possibilities are a change in the coding region of the VDR gene resulting in functionally different receptor protein or alternately a different level of otherwise identical receptor proteins.

This area of understanding the genetic influences on bone metabolism will be a major research focus in the future and provides a useful model or the assessment of genetic influences on other quantitative traits.

Other Genetic Factors

Approximately 80 percent of the protein content of bone is type I collagen and effects in type I collagen produce a clinical picture of bone fragility. Type I collagen is the product of the type I procollagen gene and defects in this gene result in osteogenesis imperfecta: a genetic disorder of bone with manifestations ranging form severe skeletal fragility and fetal death to milder forms expressing the phenotype of osteoporosis, blue sclerae and dentinogenesis imperfecta. Since mutations in the collagen gene are known to result in bone fragility it has been postulated that collagen gene mutations may play a role in some forms of familial osteoporosis. Collagen assembly is a complex series of steps involving synthesis of pro collagen, post-translational modification, assembly into the triple helical structure, propeptide cleavage and collagen self-assembly into fibrils. Studies in osteogenesis imperfecta have shown that even slight differences in amino acid sequence interfere with the triple helix formation with severe effects on bone fragility. Spotila et al studied the two genes encoding type I procollagen (COL1A1 and COL1A2) in 26 subjects with low bone mass and a family history of osteoporosis but without the full clinical criteria for the diagnosis of osteogenesis imperfecta (Spotila et al 1994). Three

of the subjects had mutations that altered the endoded amino acid. Type I procollagen gene mutations may therefore explain some cases of low bone density and fracture, and may also contribute to some extent to the population variability in fracture rates, although this has as yet not been examined. It is also possible that genetic variability in type I procollagen genes could contribute in part also to the genetic variability in bone density in the normal population. Clearly bone is a complex tissue and mutations in any of the many bone-specific structural proteins involved in mineralisation and remodelling might be associated with osteoporosis. Further exploration of the genetic factors that infleunce bone metabolism is a fertile area of current research and will provide invaluable insight into the pathogenesis of osteoporosis.

Gene-Environment Interaction

While genetic factors influence achievement and presumably maintenance of bone density, environmental factors, some of which are dealt with above, are also clearly important. How these environmental factors interact with genetic influences remains unclear, however it is likely that environmental factors such as dietary calcium intake and physical activity interact with genotype in the determination of peak bone mass in any individual (Kelly et al 1990). It is possible that the genetic background of an individual may limit or enhance the ablity of skeletal mass to respond to calcium and or exercise, or possibly other environmental factors. Evidence is accumulating for interactions between calcium intake and exercise, but as yet the role of genetics in this interaction remains to be defined.

Conclusion

Current treatment strategies for established osteoporosis are limited and the ideal lies in prevention of osteoporosis, through maximising peak bone mass and prevention of subsequent loss. Recent advances highlight the major impact of osteoporosis on the aging community and the need for rational preventative strategies at all ages. Advances in understnading the genetics of osteoporosis offer the promise of not only improving our undertsanding of the pathophysiology of this disease but may in the future allow targetting of prevention and therapy to those most likely to benefit.

References

1. Black LJ, Sato M, Rwley ER et al. Raloxifene (LY139481 HCl) prevents bone loss and reduces serum cholesterol without causing uterine hypertrophy in ovariectomised rats. J Clin Invest 1994; 93: 63-69
2. Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for prediction of hip fractures. Lancet 1993; 341: 72-75
3. Felson DT, Zhang Y, Hannan MT et al. The effect of postmenopausal estrogen therapy on bone density in elderly women. N Engl J Med 1993; 329: 1141-1146
4. Hall GM, Spector TM, Griffin AJ, et al. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis and Rheumatism 1993; 36: 1510-1516
5. Hopper JL, Seeman E. The bone density of female twins discordant for for tobacco use. N Engl J Med 1994; 330: 387-392
6. Johnston CC, Miller JZ, Slemenda CW, Reister TK, Hui S, Christian JC, Peacock M, Calcium supplementation and increases in bone mineral density in children, New Engl J Med, 1992, 327, 82-7
7. Jones G, Nguyen TV, Sambrook PN, Kelly PJ, Eisman JA. Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study. BMJ 1994 b. Vol 309:691-695
8. Jones G, Nguyen TV, Sambrook PN, Kelly PJ, Gilbert C and Eisman JA. Symptomatic fracture incidence in elderly men and women: The Dubbo osteoporosis epidemiology study (DOES). Osteoporosis International 1994 a. 4:277-282.
9. Katz I, Li M, Joffe I et al. Infleunce of age on cyclosporin A-induce alterations in bone metabolism in the rat in vivo. J Bone Min Res 1994; 9: 59-67
10. Katz IA, Epstein S. Postransplantation bone loss. J Bone Min Res 1992; 7: 123-126
11. Kelly PJ, Eisman JA. Osteoporosis-Genetic effects on bone turnover and bone mass. Annals of Medicine. 1993, 25:100-102
12. Kelly PJ, Sambrook PN, Eisman JA, The interaction of genetic and environmental influences on peak bone density. Osteoporosis International, 1990, 1, 56-60
13. Lloyd T, Andon MB, Rollings N, Martel JK, Landis JR, Demers LM, Eggli DF, Kiesehorst K, Kulin HE. Calcium supplementation and bone mineral density in adolescent girls. JAMA 1993; 270: 841-844
14. Morrison N, Cheng QJ, Tokita A, Kelly P, Cofts L, Nguyen T, Sambrook P, Eisman J. Prediction of bone density with vitamin D receptor alleles. Nature 1994; 367: 284-287
15. Morrison N, Yeoman R, Kelly P, Eisman J. Contribution of trans-acting factor alleles to normal physiological variability: Vitamin D receptor gene polymorphisms and circulating osteocalcin. Proc Natl Acad Sci (USA) 1992, 89:6665-6669
16. Nguyen T, Sambrook P, Kelly P, Jones G, Lord S, Freund J, Eisman J. Prediction of osteoporotic fractures by postural instability and bone density. B Med J 1993, 307 1111-1115
17. Pocock NA, Eisman JA, Dunstan CR et al. Recovery from steroid induced osteoporosis. Ann Int Med 1987; 107: 319-323
18. Recker RR, Davies M, Hinders SM, Heaney RP, Stegman MR, Kimmel DB. Bone gain in young adult women. JAMA 1992; 268: 2403-2408
19. Reid IR, King AR, Alexander CJ, Ibbertson HK. Prevention of steroid-induced osteoporosis with 3 amino-1-hydroxypropylidine-1,1-bisphosphonate (APD). Lancet 1988; 1: 143-146
20. Sambrook PN, Birmingham J, Kelly PJ, Kempler S, Nguyen T, Pocock N, Eisman J. Prevention of corticosteroid osteoporosis; A Comparison of Calcium, Calcitriol and Calcitonin. N Engl J Med. 1993, 328:1747-1752
21. Sambrook PN, Kelly PJ, Keogh A, Macdonald P, Spratt P, Freund J, Eisman J. Bone loss after cardiac transplantation; a prospective study. J Heart and Lung Transpl 1994; 13: 116-121
22. Seeman E, Szmukler GI, Formica C, Tsalamandris C, Mestrovic R. Osteoporosis in anorexia nervosa: the influence of peak bone density, bone loss, oral contraceptive use, and exercise. J Bone Min Res 1992; 7: 1467-1474
23. Spotila LD, Colige A, Sereda L, et al. Mutation analysis of coding sequences for type I collagen in individuals with low bone density. J Bone Min Res 1994: 6, 923-932
24. Tokita A, Kelly PJ, Nguyen T, Qi J-C, Morrison N, Risteli L, Risteli J, Sambrook P, Eisman J. Genetic influences on type I collagen synthesis and degradation: further evidence for genetic regulation of bone turnover. J Clin Endocrinol Metab . 1994; 78: 1461-1466
25. Ward RL, Morgan G, Dalley D, Kelly PJ. Tamoxifen reduces bone turnover and prevents bone loss at the lumbar spine and femoral neck in early postmenopausal women. Bone and Mineral 1993, 22:87-94
26. White C, Nguyen TV, Jones G, Morrison N, Gardiner E, Kelly PJ, Sambrook PN, Eisman JA. Vitamin D receptor alleles predict osteoporotic fracture risk. 1994: 9; Suppl 1 Abstract B 135

Emeritus Professor G. Douglas Tracy

Recent Advances in the Diagnosis and Management of Arterial Disease

Advances in the treatment of arterial disease continue to flow from better understanding of the mechanisms of atherogenesis, improving techniques for diagnosis and assessment aided by new technology, and from a wider range of operative interventions with improved outcomes.

Progress in management has also followed the development of teamwork in caring for patients with arterial disease, with the advent of vascular physicians and radiologists who specialise in endovascular procedures.

Pathogenesis

Far from being a uniform hardening of the arteries ("arteriosclerosis") atherosclerosis is a segmental condition originating in the endothelial layer of arterial intima at sites of endothelial injury. Such injury might result from a multiplicity of factors, among which are the effects of tobacco, hyperlipidaemia, hypertension, and possibly increased free radical formation from environmental pollutants and aging.

Mechanical hydraulic stress determines the location of lesions in large "arteries of distribution" at bifurcation sites especially, which often lend themselves to successful surgical intervention as the more distal "arteries of supply" can be minimally affected. Why such localisation might impact on a single carotid bifurcation, or the aortic bifurcation, at the same time sparing other sites prone to atherosclerotic disease, is still a mystery, but in all cases it behoves clinicians to carefully scrutinise the coronary and cerebral arterial supply in patients who present with peripheral arterial occlusions.

Increasing understanding of the remarkable biological activity of intimal endothelium with its capacity to secrete prostacyclin, vasodilator substances and platelet repellents on the one hand, while in the injured state to elaborate thromboxane, giving rise to platelet accretion and thrombogenesis, is gradually increasing the potential for drug interventions which favour healthy endothelial activity such as antioxidants, (See Figure 1).

The atherosclerotic lesion itself contains variable constituents including "foam cells" laden with cholesterol, platelet/fibrin aggregates, proliferating smooth muscle cells and areas of haemorrhage in the subintimal plane. The development of haemorrhage within a plaque can cause sudden swelling and rupture of the overlying endothelium producing atheroembolism or clot formation. Isolated stenotic lesions might be pultaceous and soft in consistency lending themselves to compaction or dispersal by the technique of balloon angioplasty, with

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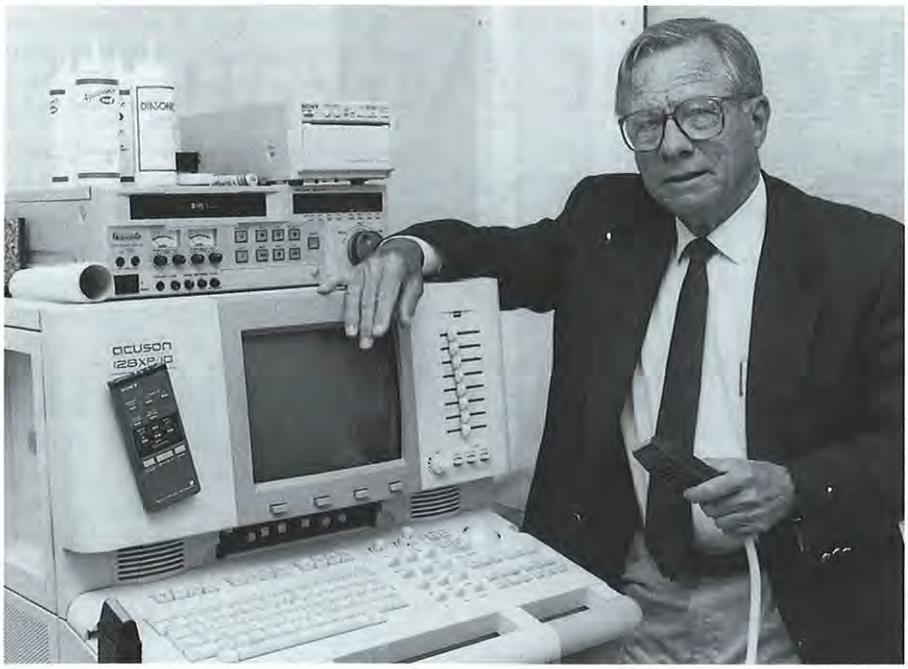

the prospect of subsequent healing by endothelial regrowth. Endothelial regeneration takes place also in the arterial conduits for bypass grafting, which are first covered with a smooth fibrin/platelet film over which endothelial cells grow, taking up to 6 months for complete coverage.

The Vascular Physician

The vascular physician is creating a new specialty in internal medicine, in parallel with the improvement in ultrasound diagnosis of arterial and venous disorders. The role of the vascular physician is invaluable in patient assessment to evaluate cardiac and cerebrovascular disease, modify risk factors which play a part in atherosclerosis, and detect an increasing range of diagnosable coagulation disorders, as well as hyperviscosity and microvascular problems.

Ultrasound Diagnosis

Rapid improvements in ultrasonography have established the vascular laboratory as an essential component of the diagnosis and management of arterial and venous disease. This safe, non-invasive technique allows colour duplex imaging of the large arteries and veins with ever increasing precision. This has almost eliminated the need for invasive angiography in many cases and in the progress assessment of patients both before and after surgery. In some cases it is sufficiently precise to allow surgical treatment without the use of angiography, (See Figure 2).

Angiography

Angiography too has made great strides in comfort and safety in the last decade with the introduction of digital subtraction angiography. With the insertion of fine catheters - usually in the brachial artery - under local anaesthesia, the digital subtraction technique provides excellent visualisation of blood vessels with much smaller dosage of contrast media, minimising the erstwhile hazards of nephrotoxicity, fluid overload, and other complication from the large bolus of dye. Dosage is still a factor in limiting the range of arterial visualisation so that it is still not sufficiently safe to combine cerebral, cardiac and peripheral visualisation. However the modern D.S.A. is usually a comfortable procedure performed in the X-ray Department without the need for hospital admission. Skill in arterial catheterisation has led some radiologists to become experts in the newer endovascular techniques for dealing with isolated lesions. Of these the most common is balloon angioplasty, in which a catheter is placed through the lesion under vision, and a sausage shaped balloon of fixed geometry blown up to compress the lesion and relieve the arterial stenosis. This is especially valuable for localised stenosis in large arteries such as the iliac and femoral arteries. Other endovascular techniques, including the laser probe and atherectomy drill are still in the developing stage and the results thus far have been disappointing. Further extensions of endovascular techniques include the use of an intravascular stent which embeds itself in the wall of the artery to produce expansion of stenotic sites. Success with this technique has led to the recent concept of endovascular grafting for large vessel aneurysms - a technique still in the evaluation phase.

A further place for the interventional radiologist with arterial catheterisation is in the direct application of thrombolytic therapy by the "pulsed spray" technique, where a catheter is passed to the site of thrombosis for the infusion of thrombolytic agents with the effect observable by intermittent angiography. Thrombolytic therapy is most useful in the first few hours of acute thrombosis, but is usually unsuccessful 12 to 24 hours after the clot has developed.

Arterial Surgery

Notwithstanding the advances in management based on earlier diagnosis, control of risk factors, and balloon dilatation performed on a day patient basis, operative treatment is frequently indicated for symptoms such as limiting claudication, or the appearance of severe ischaemia with nocturnal rest pain, or toe lesions threatening the onset of gangrene. In recent decades there has also been a huge increase in carotid artery surgery for the prevention of stroke. The onset of actual stroke usually rules out arterial surgery as the damage is irreversible and any revascularisation is likely to cause haemorrhagic complications in brain infarction. However clinicians now are alert to the harbingers of strokes such as transient ischaemic attacks with fleeting episodes of blindness or unilateral paraesthesiae or weakness which might only last for minutes, but which might be accompanied by the telltale bruit of carotid stenosis.

A variety of surgical techniques are available to deal with localised arterial

obstructions, but selection of the best technique often cannot be determined until surgical exposure, as the actual state of the arteries cannot always be determined by the luminal images of angiography. Because the atherosclerotic plaque develops in the intimal layer of the vessel, localised lesions can often be removed successfully by the technique of endarterectomy, which leaves a clean plane at the level of the internal elastic lamina with a relatively normal arterial media and adventitial coat. This is the technique usually used in carotid surgery, where to avoid stenosis in small arteries (especially in women) a patch graft might be used. Satisfactory endarterectomy in large arteries however usually leaves a soft, rather large vessel which can be closed without compromise of diameter. Endarterectomy as an isolated procedure is less often applicable to the lower limb arteries because of more extensive atherosclerosis which makes it difficult to gain a satisfactory "endpoint" after endarterectomy. For proximal arterial disease in the aorto-iliac segment the most common procedure is an aorto-bifemoral bypass graft using prosthetic material. According to circumstance, the surgeon usually selects a bifurcated tube of Gore-tex, or a knitted dacron graft impregnated with protein to prevent blood leakage. Such bypasses often entail concomitant endarterectomy at the site of anastomosis especially at the common femoral artery bifurcation.

Below the groin bypass techniques are most commonly employed, using for preference the patient's own saphenous vein if it is of good calibre. Thin walled Gore-tex can also be used successfully for bypass grafts to the popliteal artery above or below the knee. When there is occlusion of the popliteal artery with leg threatening critical ischaemia, amputation might be averted by the use of a long bypass graft to the tibial or peroneal arteries. In these circumstances the preferred bypass is the saphenous vein - often using an in situ technique with disruption of the saphenous valves, ligation of the tributaries, and distal anastomosis using optical magnification for the small anastomoses (sometimes also using an Esmarch tourniquet to create a bloodless field so that vascular clamps need not be applied to the small peroneal or tibial arteries). Success of such bypass procedures relies upon the capacity of the "run-off" circulation and the state of the arteries to which the distal anastomosis is made. In diabetics with calcification of the tibial vessels, such bypasses are less successful. In some circumstances surgeons might be successful with a combination of techniques, such as the use of an endarterectomised segment of artery joined to a Gore-tex prosthesis for the necessary length of bypass.

For distal small artery anastomoses a segment of saphenous vein may be combined with prosthetic material in the upper part of the leg to achieve successful bypass. (Figure 3).

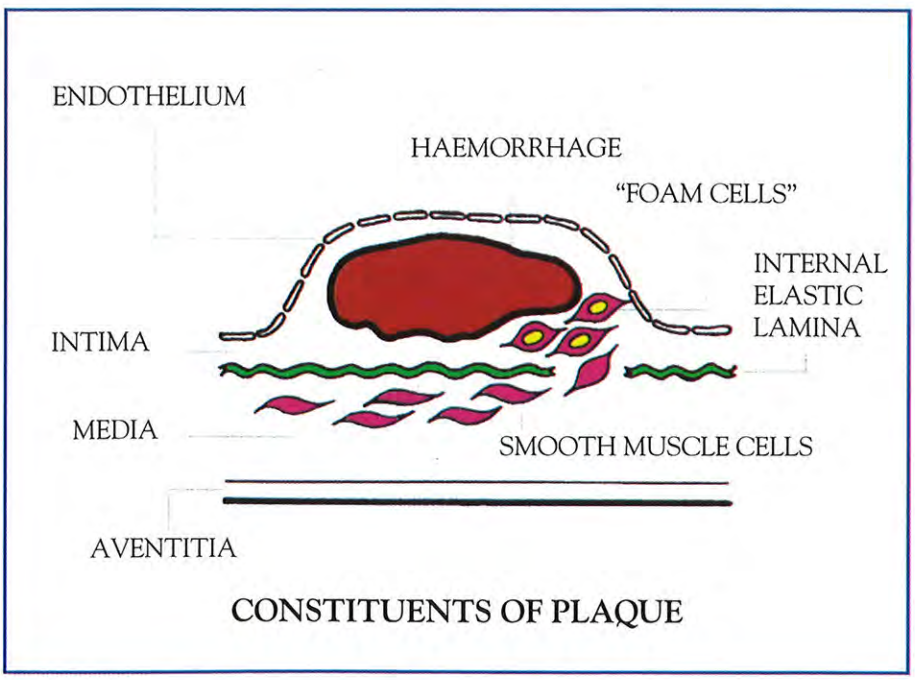

Figure 1. Diagram of major constituents of atherosclerotic plaque

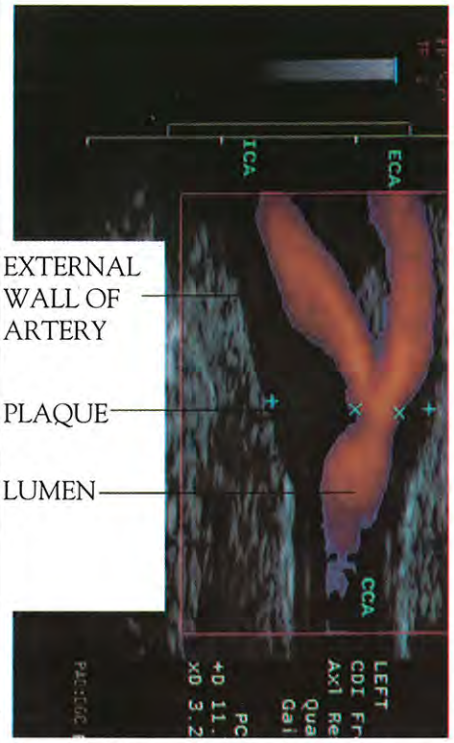

Figure 2. Showing colour duples sonography of carotic stenosis.

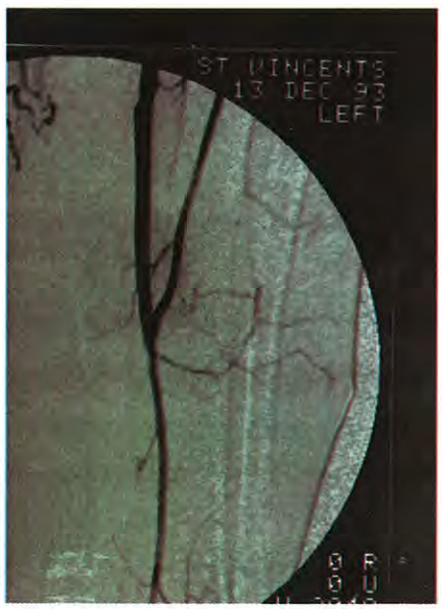

Figure 3. Digital subtraction angiogram of femoro-tibial bypass

SUMMARY

This review of recent advances in the diagnosis and management of arterial disease outlines the advantages that have followed a team approach to vascular diagnosis and management including a vascular physician, a vascular laboratory with improved ultra-sound imaging, advances in angiography technique, endovascular balloon dilatations for localised stenoses and a broadening scope of arterial intervention for more extensive obstructions in large arteries.

The St Vincent's Clinic Foundation

One of the goals of the new St Vincent's Clinic is to provide the highest standard of patient care that is attainable. At the same time we strive to collect and analyse available data for clinical research

Although government and other research bodies give some financial support for basic laboratory work for full-time researchers, there is sparse funding for the prosecution of clinical studies conducted in the course of patient care, upon which evaluation of all new treatment modalities depends.

The St Vincent's Clinic Foundation has been created to meet this important need (with appropriate legal status and tax deductibility for donations) and we seek your support to ensure that our aims are fulfilled for the clinical advantage of all patients. The next page details recipients of Clinic Foundation grants.

These pages summarise the clinical studies currently being supported by the Clinic Foundation.

1. Professor Terry Campbell - Clinical Pharmacology

"Mechanisms of Hypertension"

High blood pressure is still the most common morbid condition in the western world. Its complications such as stroke and heart attack are the biggest killers in our society. Despite much progress, the underlying mechanisms of high blood pressure are still unknown in most patients. This study deals with the function of the muscle cells in the walls of blood vessels. No matter what the basic stimulus, increased tension in these cells is the contributing and probable causal factor in the development of high blood pressure. Sophisticated electro-physiological recording techniques are used to study movements of molecules in and out of these cells and the mechanisms by which this is modulated.

2. Dr Brett G Courtenay - Orthopaedics

"International Documentation and Evaluation System for the Assessment of Hip Replacements"

The Clinic Foundation grant has enabled the Orthopaedic Department to establish a computerised data base on joint replacements, including a digitised camera to store X-rays with the data base. This has made possible detailed outcome studies for St. Vincent's Private Hospital that will measure the performance of joint replacements over the short and long term.

3. Professor Michael P Feneley - Cardiology Department

"Non-Invasive Measurement of Left Ventricular Pressure-Volume Relationships and Derivative Indices of Contractility"

At present accurate measurement of the heart's pumping function requires insertion of various measuring devices during the procedure of cardiac catheterisation. This project is to devise methods for these measurements to be made in a completely non-invasive fashion, combining measurements of the heart pumping changes by ultrasound, integrated with pressure measurements through the skin overlying an artery. The combination of these two measurements into a single measure of the heart's pumping performance has been completed, providing a simpler, safer and cheaper method for assessing the heart's pumping performance, which can be used repeatedly in patients with all cardiac disorders.

4. Dr David Golovsky - Department of Urology

"Construction of Recombinant Immunotoxins from Tumour Associated Lymphocytes in Renal Cancer"

This project aims to construct recombinant immunotoxins from lymphocytes associated with kidney cancer. Excellent

progress has been made with completion of phase one by successful achievement of artificial tissue cultures of renal cell carcinoma - itself a most difficult feat. The next phase of the study will involve the injection of human lymphocytes into the cancer cells implanted in mice - with the ultimate hope of culturing immune lymphocytes in a bio-reactor, so that treatable quantities of lymphocytes can be obtained for clinical trial in cancer patients.

5. Dr Paul J Kelly - Department of Endocrinology

"Calcitriol in the Prevention of Bone Loss Following Cardiac Transplantation"

Prevention of bone loss following cardiac transplantation: Corticosteriods used in transplant operations sometimes have the complication of producing major bone thinning or osteoporosis. This study involves the use of an active from of Vitamin D, (Calcitriol) to try to prevent such bone loss. It involves bone density scans performed each six months for two years and already 30 patients after transplantation have commenced this study.

6. Professor L Lazarus, G Smythe, D Hodgson and J Casey - Department of Endocrinology

"The Use of Mass Spectometry in the Diagnosis of Nonclassical Congenital Adrenal Hyperplasia"

The study of the use of mass spectrometry in the diagnosis of congenital adrenal hyperplasia has led to the development of original techniques for the identification of a wide range of steroid hormones. Apart from more specific diagnosis of endocrine disorders, these studies may be highly relevant to the measuring of steroid hormones in minute elements in race horses and Olympic athletes. It offers the prospect of suitable androgenic steroid assays for use in the year 2000 Olympic Games.

7. Professor R Lord and Dr Alan Meek - Department of Vascular Surgery

"An Investigation of Acute Platelet Kinetics Following Endarterectomy and Patch Angioplasty in Sheep"

In many arterial operations an arterial patch is used to avoid narrowing of the arterial segment. These patches, from a variety of materials, can react with the blood stream to form a platelet layer with the potential to cause additional problems. These studies quantify the thickness of this layer by labelling platelets with a radio-active isotope which can then detect the amount of platelet deposition on the arterial patch. Excellent progress has been made in the study of preferred patch materials, and also in the study of substances given to patients which may further reduce platelet deposition.

8. Dr Terence O'Connor - Colorectal Department

"Faecal Oncogenes"

Colon cancer is the most common internal malignancy affecting one in 25 Australians at some time in their life. Because it begins silently, 60% of patients succumb from this cancer despite treatment. If the cancer can be detected when still confined to the bowel wall 90% will be cured. This makes critical the importance of early diagnosis and this study in conjunction with Dr Robin Ward from the Haematology Department is designed to detect molecular genetic mutations in cancer cells isolated from a stool sample. This would be an important advance and the project presently focuses on the most economical and reproducible screening test to detect such genetic change so that patients may be identified at the early curable stage of this disease.

9. Professor Michael O'Rourke - Cardiovascular Medicine

"Non-Invasive Measurement of Arterial Pressure"

This project is concerned with non-invasive measurement of arterial pressure, which permits measurement of the hydraulic load of the heart, as well as indices of heart function - including duration of left ventricular ejection and capacity for myocardial perfusion, combined with other vascular properties. The first task for these studies was to determine the effects of exercise on the heart and has already given rise to 12 publications since the inception of the study, performed in conjunction with the Department of Nuclear Medicine at the Clinic.

10. Dr Nicholas Pocock - Department of Nuclear Medicine

"Assessing Prediction of Hip Prosthesis Loosening"

A study on the prediction of loosening of artificial hips has been initiated through the aid of Clinic Foundation grant. Hip replacements for arthritis have been one of the greatest advances in orthopaedic surgery and has allowed many individuals to maintain active lifestyle. While highly successful in most cases, a small number develop loosening and may need replacement surgery.

Identifying those patients in whom loosening is likely to occur is an important need and this study used x-ray techniques to measure bone strength immediately adjacent to artificial hips. As well as allowing identification of patients likely to develop loosening, the study may help to improve artificial hip design to reduce this likelihood of loosening even further.

11. Dr Janet Rimmer - Department of Thoracic Medicine

"Inflammation in Asthma"

Asthma is a common disease in Australia which appears to be increasing. All asthmatics have typical inflammatory changes present in the airways. This project is designed to establish simple blood tests which would give a measure of asthmatic airways inflammation. So far studies of the activity levels of types of cells which play a key role in the inflammatroy process measured in normal subjects, allergic subjects and allergic asthmatics. To date these tests are not yet sensitive enough to distinguish between the different groups and the study is being extended in severe asthmatics to develop more sensitive tests for this important distinction.