Osteoporosis: a family affair

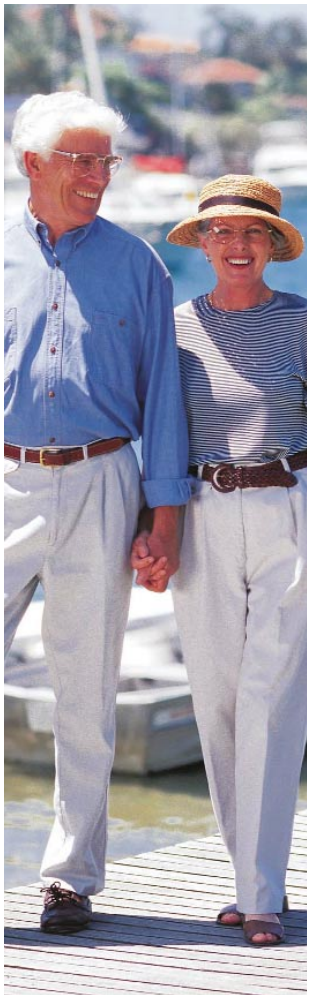
The magnitude of the problem

Osteoporosis (or fragile bones) does not cause symptoms until fractures occur (often following minimal trauma). These osteoporotic fractures are a major and increasing public health problem in Australia. Population data from Southern Tasmania has suggested that 45% of women and 28% of men can expect to experience at least one fracture between the age of 50 and death. Currently there are between 50,000 and 75,000 fractures per annum due to osteoporosis in Australia each year costing just under $800M in direct health care costs. Secular trends suggest this number is going to triple in the next 50 years placing a major strain on our health system. To date, prevention programs have concentrated on the menopause and the elderly (where falls prevention is also important) but might there be other ways of preventing this disease that will affect many of us?

Childhood prevention

More than 20 years have passed since Dent proposed that senile osteoporosis is a paediatric disease. Since that time evidence is slowly accumulating that it may be possible to modify risk of osteoporosis in later life by changes in early life. Peak or maximal bone mass is obtained at about age 16 in girls and 20 in boys with some additional small gains up to the age of 30. Bone density interpretation in later life depends largely on the absolute reduction in bone mass as compared to peak bone mass rather than compared to those of the same age. Variation in peak bone mass has been estimated to contribute approximately 50% of the variation in bone mass in the elderly. Peak bone mass has a number of known determinants. These include genetic factors, physical activity and diet (particularly calcium intake) but there is limited information on other factors.

Genetic factors explain 60-80% of the variation in bone mass. The child of a mother with osteopaenia (thin bones) has a 5% decrease in bone mass compared to other children. Physical activity currently appears the most important environmental factor. In adult life, weight bearing exercise can maintain bone mass or, at most, lead to small gains. In childhood, particularly in the prepubertal years, exercise can be associated with large gains in bone mass. In gymnasts, bone mass can be 10-15% higher than controls and at least some of this is maintained into adult life. This is likely to represent the maximum achievable gain in bone mass. In less selected eight year old children from Hobart, both sports participation and endurance fitness were associated with 5-10% higher bone mass which reflects what may be achievable at a population level. The cur-



rent trends to decreased physical activity are of particular concern for bone development and there is a strong need to limit television watching, computer time and video games. The role of exercise during puberty is controversial as excess may lead to additional problems such as amenorrhoea potentially offsetting any gains. However, it is unclear what constitutes excessive exercise at present with regard to bone and this will vary from person to person. The role of diet also remains controversial. The controlled trials that have been done to date have differing conclusions but have generally shown little long-term benefit from calcium supplementation alone although a recent trial of milk supplementation in adolescent girls was superior to calcium alone suggesting a possible role for growth factors. We have recently reported that potassium intake was also associated with healthy bones in children. There are, however, problems with accurately measuring dietary intake in children leading to diet (calcium and other nutrients) being a major area of uncertainty at present.

Other factors may well be involved. One of these is vitamin D. The major source of this is sunlight thus, in most areas in Australia, deficiency is unlikely to be a problem in children. In Hobart, however, UV levels fall markedly in the winter months and we have documented a dose response relationship between winter sunlight and bone mass in prepubertal children suggesting that ensuring adequate vitamin D levels in children is important in the more southern latitudes (and in the elderly at all latitudes). Cigarette smoking is deleterious to bone in adults particularly in males and women after the menopause. There is a paucity of data on smoking in children which may be harmful particularly given that the average age of starting is now well before attainment of peak bone mass. Passive smoking is unlikely to be harmful to bone due to inadequate levels of exposure. Reports on teenage eating disorders have been conflicting about long term deficits in bone mass.

Early life exposures appear to influence the risk of cardiovascular disease and diabetes in later life. Recently, intriguing evidence has emerged that very early life exposures may have a similar effect on the risk of osteoporosis in later life. Cooper in the UK has shown that weight at one year is associated with bone mass at age 20 and 70 in separate population samples. Exact mechanisms for this are unknown but the suggestion has been made that programming of growth and bone mineralisation may occur either in-utero or in the early postnatal period. Some suggestive data is available for a possible protective role of breast milk in both pre-term and term children. Data is also available on smoking during pregnancy by the mothers which has a long-term deleterious effect on bone mass in 8 year old children. This effect appears to be mediated through impaired placental function rather than socioeconomic factors. Maternal diet during pregnancy also appears important with evidence supporting a beneficial role of magnesium and phosphorus and a negative role for fat. Analysis of results in our Hobart cohort indicates that smoking, diet in-utero and breastfeeding can explain up to 10% of the variation in bone mass at age 8 which is similar to the amount that can be explained by physical activity and diet suggesting that osteoporosis may well have its origins in early life although there is a need to follow these children at least until age 20 to check that the rapid changes that occur during puberty do not overwhelm any early life effects.

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Treatment of osteoporosis

Why treat osteoporosis - it is never too late

Fractures due to bone fragility affect up to 50% of women and 30% of men in their life time. Fractures result in increased morbidity and mortality and they predispose to more fractures. The risk of fracture within 12 months of sustaining a fracture is about 30%. Bone loss predisposes to fractures and as we age the rate of bone loss accelerates, it does not decelerate so that in old age the declining mass of bone declines proportionally faster, like watching a block of ice melting in the last stages before it disappears.

The most important reason to treat elderly persons is that we have drugs that can prevent this progressive loss of the skeleton and these drugs work quickly, even in the elderly, the risk of fracture can be reduced by about 50% within 12 to 18 months of starting treatment. It is never too late.

The need to prevent and treat osteoporosis is great because of the growth of the ageing population. More women and men are living to enjoy old age but with this comes the illnesses of old age, the increased risk of falls and fractures. The rise in the numbers of elderly in the world means more and more individuals will be at risk of fracture and it is clear that the health burden of fractures will impose a huge financial burden on communities throughout the world. Fractures are occurring faster than our ability to prevent them so zero fracture tolerance is a goal yet to be achieved.

The aim of treatment

The aim of treatment is to prevent the development of osteoporosis and to reverse the structural damage that has occurred in those women with osteoporosis - ie, to rebuild the skeleton. There is excellent evidence that we have drugs that can prevent bone loss and prevent the continued structural damage that occurs during ageing in women, and in men. The evidence that we can rebuild the skeleton is coming (see below).

The scientific world in collaboration with industry and governments have been successful in reducing fracture risk by 50 to 60% in persons at high risk of fracture. We can reduce the occurrence and the progressive increase in the porosity of bone, we can slow bone loss and so prevent the thinning of the cortical shell that supports to the muscle mass moving the skeleton and the person it is holding up against gravity.

We can prevent thinning of trabeculae and loss of interconnecting trabecular bone that forms the honeycomb structure of the trabeculae plates and sheets. It is these interconnecting plates and sheets of mineralized bone that make the skeleton a masterpiece of engineering. The perfect marriage of form and function, using the minimum amount of material for maximum function (unlike marriage that does the opposite).

The motionless world

This lightness of being allows great speed and mobility, an evolutionary requirement for survival when we needed to find lunch or flee to avoid being lunch. All this has changed, perhaps for the worse from the skeleton's point of view as we live in a concrete jungle, a virtual world of elevators, escalators, moving platforms, in dial a dinner, beam-me-up Scotty, please fasten your safety belt, bring your seat to the vertical position. We move in a clutch less automatic digital world of the remote control, avoiding movement across any distance, even between couch to TV. The green planet has shrunk as we can be relocated, entertained, fed and watered without any movement of the musculoskeletal system whatsoever.

We probably don't deserve a skeleton and should be soap suds or jelly fish, but for now we still have the mortal enemy, gravity and we need to develop drugs that not only prevent the development of osteoporosis - ie, prevent

bone loss, we need drugs that can rebuild the skeleton, reconnect and thicken the trabeculae, thicken the cortical shell by depositing new bone on the outside like a coat of paint on a weather beaten house, deposit bone on the inside of the cortex so that it becomes thicker, and reduce the numbers and size of the pores in the cortical shell that give osteo -poro-sis its name so that when falls occur the femoral neck does not crack as it does when a hip fracture occurs.

We need drugs to restore the loss of elasticity of the bone by depositing collagen, the protein fibre that forms skin and bone. It is this tissue that gives elasticity to the skin so that it can stretch when we bend our elbows to eat, drink and be merry. It is this fibre that also gives elasticity to bone but nature realized that an elastic band is no defense against gravity.

As we emerged from the primal waters of evolution we had to stiffen the skeleton so that it could traverse the surf and sand, climb the tree and then descend as eating nuts, roots and leaves was not to be our way. Nature sprinkled the elastic collagen with diamonds, the sparking crystals of calcium hydroxyapatite to reinforce the tissue giving it that perfect harmonious balance between elasticity and stiffness so that it can tolerate load without bucking and cracking.

Drugs are needed to restore the bone material, the collagen matrix, and its mineral content to ensure that the bone stiffness is sufficient to tolerate loads but not to the point where it is too stiff so that the elasticity is lost. When loaded, the bone must be able to absorb energy by compressing then rebounding like a spring absorbs the bumps in the road.

Has there been progress, yes. Can we restore elasticity and stiffness, yes. Has this been done, yes. Ten years ago we had very few drugs that could be used to prevent or slow down bone thinning. Today we have drugs that prevent bone loss and reduce the chance that a fracture will occur by about 50%.

The work of science, industry and governments

Science knows no boundaries, It is the universal language that makes strangers acquaintances, acquaintances friends, new friends old friends, and old friends give life immeasurable richness. Hundreds of scientists have worked together in collaboration with industry and governments to develop new drugs for the treatment of osteoporosis. This effort has to a large extent been successful and continues to be so.

Because of the strong collaboration between hundreds of scientists large studies have been done, often involving 10,000 to 15,000 patients studied for several years to help determine what is the best treatment to prevent bone loss and fractures. We have strong evidence that drugs like the bisphosphonates alendronate and risedronate, and the selective estrogen receptor modulator, raloxifene reduce the risk of fractures.

A reduction in risk for spine fracture using alendronate, raloxifene and risedronate occurs early in treatment, within the first 12-24 months. These drugs reduce the risk of single or multiple spine fractures, they reduce the risk of painful fractures, reduce the occurrence of back pain and disability, loss of independence, keep us out of nursing homes, a fate worse than death itself, and shorten the stay in the dehumanized sanitized white washed hospital wards. These effects are documented in women with osteoporosis for alendronate, raloxifene and risedronate.

Non-spine (limb fractures, pelvis, forearm, humerus) fractures are also reduced with alendronate and residronate, but there is no evidence for this with raloxifene. The risk of hip fracture is reduced with alendronate and risedronate but most of this evidence is in women under 80 years of age. More work is needed as we still lack evidence that drugs reduce the risk of fracture in women over 80 years of age (about 50% of all hip fractures occur in this group).

Falls are a most important cause of fractures of the hip and other long bones so that ways of reducing the frequency and the severity of falls in this concrete jungle are needed. We know that wearing a hip protector reduces the incidence of hip fractures but there are problems with

compliance; my late father at 83 years felt he was too young for such a device. Vitamin D deficiency can predispose to muscle weakness and falls. Vitamin D deficiency is common in the elderly, especially elderly residents of nursing homes and vitamin D this is easily correct by giving a supplement with food our by increasing sunlight exposure in the early part of the day or the late remains of the day.

We have other drugs for the prevention and treatment of osteoporosis such as estrogen, etidronate, calcitonin, vitamin D metabolites. Some of these drugs may prevent fracture, but, for historical and other reasons, flaws in the way the studies were carried out (with small numbers of participants, short duration of the studies and other factors) that our confidence in the effectiveness of the drugs is less.

It is possible and indeed likely that that hormone replacement therapy reduces the risk of spine fractures but the evidence is not as reliable compared with the evidence for the other drugs. The effect of hormone replacement on hip fractures and other nonvertebral fractures is weak.

How do the drugs work?

Drugs like alendronate, risedronate, raloxifene and estrogen are called antiresorptive agents. They slow or abolish the progressive thinning of bone but are unlikely to restore bone architecture. The drugs slow down the rate at which the skeleton is renewed. The existing bone continues to mineralize, ossify, and so becomes more and more densely laiden with calcium crystals which to a point may increase the strength of the bone. When these drugs are given some of the bone that would normally be removed is not and it becomes more densely 'packed' with mineral due to changes in the crystal size in the bone. As with many good things in life, sometimes too much is not a good thing. It is possible that the increase in mineral content of the existing bone can be too much so that the fine balance between the elasticity of the bone and the stiffness is lost and the bone becomes too stiff with too much crystal and this can change the from being elastic to being too stiff so that it may crack. We have a lot to still learn about how long these drugs can be given.

Anabolic or bone building with parathyroid hormone therapy

As the antiresorptive drugs only slow the progressive thinning of bone rather than rebuilding it, we need drugs that actually rebuild the skeleton, and some evidence for rebuilding the eroded aged skeleton has become available with the study of the anabolic (building up) agents, particularly with parathyroid hormone (PTH). This is the most exciting advance that has taken place in the study of drugs in this field

Rapid changes rarely occur in science and the anabolic effects of PTH have been known to exist for about 70 years or more. It is only in the last 5-10 years that data has emerged that provides very consistent and encouraging results in animals and humans. One important study was published recently that suggest this drug will be useful in the management of osteoporosis. A multinational study of 1637 postmenopausal women with prior vertebral fractures to PTH reported that the risk of a spine fracture was reduced by 70% within 18 months of treatment. Nonvertebral fracture risk was reduced by 50%.

The future

The future is bright, like each morning brings the promise of new opportunities leaving the burdens of evening to memory only. There is no question that progress has been made through the international collaborations of the scientific community. Some advances become immutable but many are fire crackers that light up the night with a big bang that fizzle with a whimper. The rigours of science demand replication and cautious inference. We have progressed but we must recognise that we are far from zero fracture growth; drugs reduce but do not eliminate fracture risk, most patients who sustain fractures are uninvestigated, untreated, or mistreated. In many countries and in the minds of many, osteoporosis is just the inevitable consequence of old age and this ingrained misunderstanding needs to be fought. We have safe and effect ways of measuring bone mass, of treating high risk individuals and reducing risk for fracture even in the elderly. The work of eliminating fractures requires the collaboration of scientists, governments, industry and many if not most of the disciplines of medicine science. The notion that treatment should be given only after the first fracture is as unacceptable as treating hypertension after the first stroke or hypercholesterolemia after the first myocardial infarct and this must stop. Fragility fractures are not going away.

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