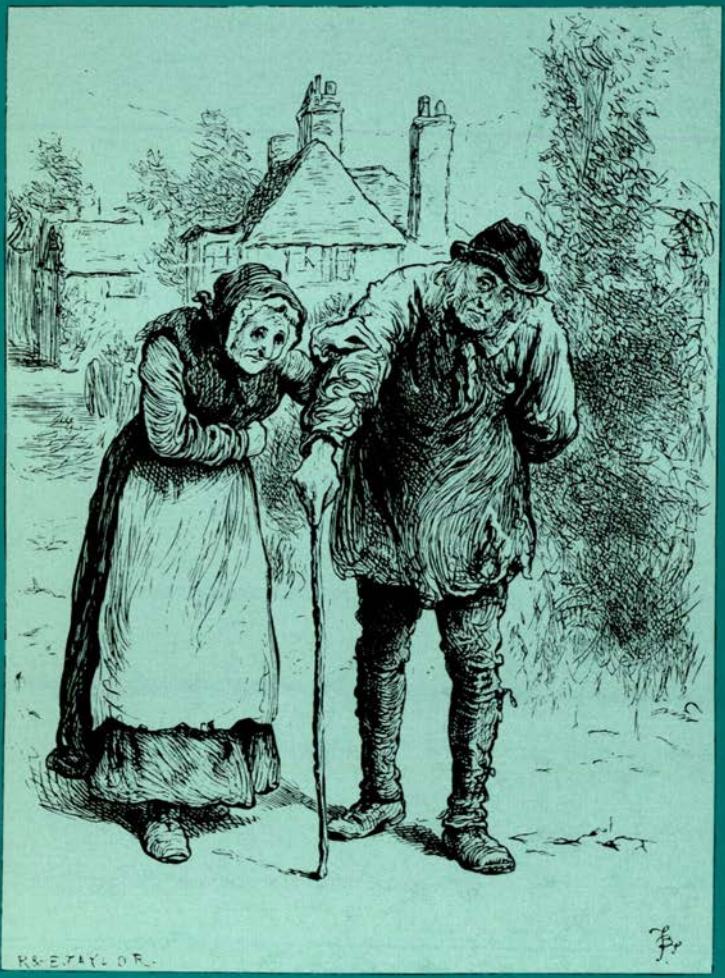
OSTEOPOROSIS

and the risk of fracture



OSTEOPOROSIS

and the risk of fracture

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Office of Health Economics

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Introduction

Osteoporosis has been a long recognised disorder even if its causes have not. Research undertaken by Little (1973) found examples from as early as the sixth century AD when Paulas Aeginata described a condition of the bone typical of osteoporosis. He also referred to non-healing hip fractures and vertebral 'arthritis' the result of a 'weakness of the parts'. In 1824 Astley Cooper stated that in old age bones 'become thin in their shell and spongy in the texture', he also noted that fractures of the neck of femur (hip) often followed moderate trauma. Whilst many physicians, even before the discovery of the X-ray in 1895, were aware that the bones of the elderly often became thin and fragile (Gordon *et al*, 1976) it was not until 1940 that osteoporosis was linked with the post-menopausal state (Fuller Albright *et al*, 1941).

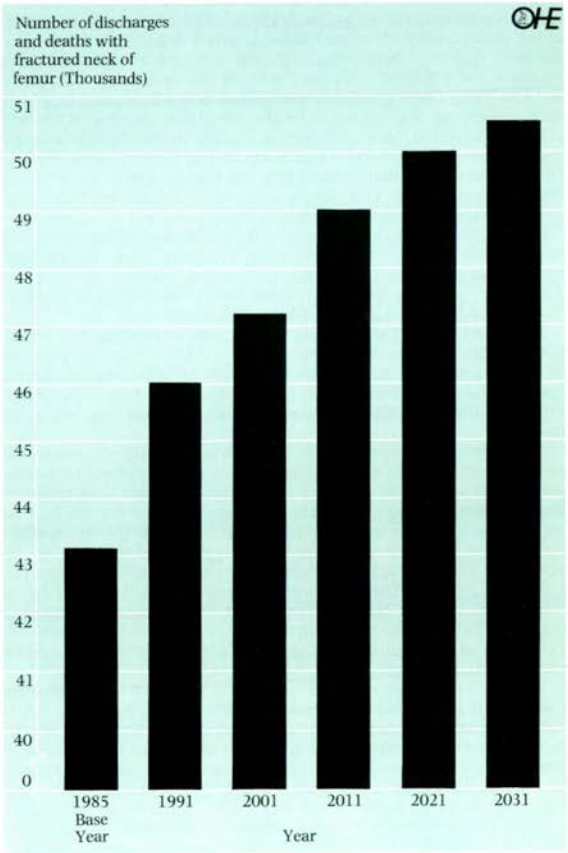
Only in recent years has the scale of the problem of osteoporosis been recognised by health care professionals. This may in part be explained by the fact that osteoporosis and its related fractures are a multi-disciplinary problem, that is it crosses several specialities in medicine including orthopaedics, geriatrics and gynaecology.

The most obvious manifestation of osteoporosis is a fracture, usually of the vertebrae, wrist or hip. Osteoporosis and its related fractures are an increasing health and economic problem and this booklet concentrates on the risks of osteoporotic fracture, the prevention of these fractures and the socio-economic costs of both fractures and preventive measures.

An increased life expectancy has led to a growing elderly population. As life expectancy has increased so have the diseases of elderly people, particularly women. Women are especially vulnerable to osteoporotic fractures not only because of the link between osteoporosis and the menopause but also because more women survive to the age at which osteoporotic fractures occur than men. It is projected that by 2031 the number of elderly people (over 65s) in the United Kingdom will be 13.6 million (22 per cent of the total population) as compared with 9.6 million (16 per cent of the total population) in 1987 (Annual Abstract of Statistics 1989). The growth in population of 4.3 million between the two years can almost entirely be accounted for by an increase in the numbers of the elderly.

The result of this increase in population in terms of the number of hip fractures (the most expensive osteoporotic fracture) occurring can be seen in Figure 1. Even on the conservative estimate that the discharge rate does not increase (there will in fact be a shift towards a more elderly population) it is estimated that the number of hip fractures in England and Wales will be 50,581 an increase of 17 per cent (7,351). The true figure may be much higher. Without therapeutic and prophylactic intervention, the economic and social costs of osteoporosis will continue to rise in the years ahead.

Figure 1 **Estimated number of cases of fractured neck of femur using 1985 annual discharge rate of 9.2**



Source HIPE 1985 and Annual Abstract of Statistics.

The nature of bone

Bone is an organ, it gives shape to the body, supports its weight, protects its vital organs and permits movement by providing attachments for muscles to act as levers. The main components of bone tissue are tiny crystals of calcium and phosphorus embedded in a framework of interlocking protein fibres (the bone matrix). These protein fibres are made primarily of collagen and it is these fibres which give bones their relative flexibility. The calcium crystals give the bones strength, hardness and rigidity (Notelovitz *et al*, 1982).

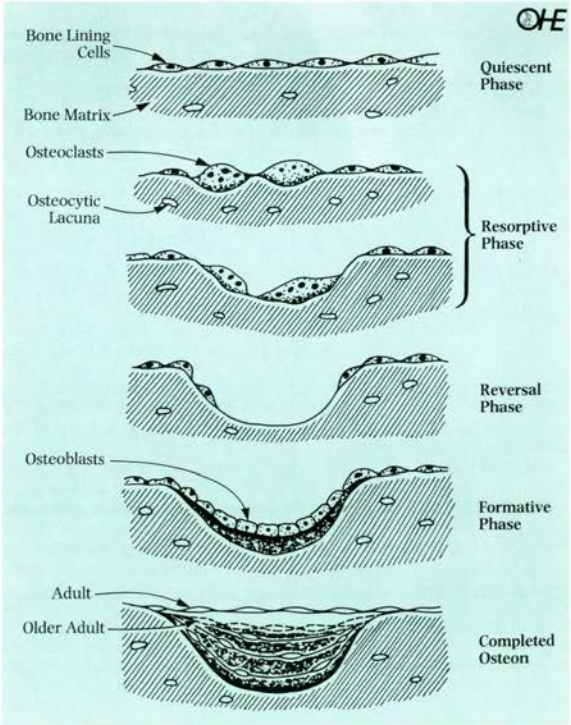
Like all living tissue, bone is constantly being broken down and reformed. New bone formation is required for growth, for repair of microscopic fractures resulting from everyday physical stress and for the replacement of worn-out bone. Whatever its age the skeleton is being continuously removed by osteoclasts and being replaced by osteoblasts (Figure 2). The bone-remodelling cycle begins with a small amount of bone breakdown. The osteoclasts, the bone resorbing cells, dig microscopic cavities along the inner surfaces of the bone. These cavities are then filled in with new bone by the osteoblasts, the bone forming cells. Many osteoblasts are required to replace the bone removed by one osteoclast. Once the osteoblasts are in place they produce the collagen matrix of the new bone. This process takes approximately ten days after which time the calcium and phosphorus crystals are laid down in the framework, bone mineralisation.

The entire cycle lasts approximately two to three months (Smith, 1987). It is estimated that adults have 10 to 30 per cent of their bone replaced each year through this process. Renewal is most rapid in the young who are still growing when more new bone tissue is produced than is lost through bone breakdown. Where bone mass is constant, in the young adult, the two processes of formation and resorption are closely balanced.

Bone grows, maintaining approximately the same shape from before birth to maturity but can respond to physical forces at any age, and if broken will repair itself as nearly as possible to its original state. The first phase of bone growth begins with the embryo. Undernourished mothers tend to produce babies with weak, under mineralised bones unless their diets are supplemented with calcium. Evidence from studies in monozygotic twins born dissimilar due to 'placental steal syndrome', where as a result of an abnormality one embryo receives the majority of the placental blood supply indicate that deprived embryos may not fully make up the difference in later life (Woolf *et al*, 1988).

The second phase is from birth to the final fusion of the epiphyses (the spongy extremity of a bone, attached to it for the purpose of forming a joint with the similar process of another bone) in late adolescence. Children's skeletons enlarge because the amount of new tissue formed on the outer surfaces of the bone (periosteal) exceeds that broken down on the inner surfaces (endosteal). Adolescence brings about an acceleration in growth that is related to the surge in sex hormone production at this time, which stimulates the formation of new bone on the periosteal. The

Figure 2



The remodeling sequence of bone is initiated by osteoclastic resorption of indeterminate duration followed by the absence of osteoclasts or osteoblasts (the *reversal phase*). Subsequently, osteoblasts appear within the resorptive bay (Howship's lacuna) and synthesize matrix (the formative phase) until a new packet of bone (the osteon) is produced. In non-growing young adults the amounts of matrix resorbed and synthesized are in equilibrium. In older individuals, on the other hand, the amount of new bone is less than the amount removed, resulting in a net decrease in skeletal mass or osteoporosis.

Source Bone and Mineral Research Annual 2. Peck W A (ed). 1984 (Reproduced by kind permission of Elsevier Press).

BOX 1

Types of Osteoporotic Fracture

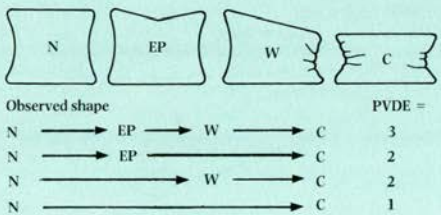
Fracture of Neck of Femur

In the elderly the neck of femur may fracture at any of four sites, usually following quite minor trauma, a fall from no more than standing height. The four sites are sub-capital, transcervical, basal and intratrochanteric. Sub-capital and intratrochanteric being the most common. A sub-capital fracture is a fracture of the femur through the neck immediately distal to the head of the bone, a intratrochanteric fracture is a fracture through the base of the neck and the trochanters of the femur, of the two the latter is the most frequently seen (ratio 2:1) (Nordin *et al*, 1984).

The age-specific incidence rises steeply with age in both sexes with women being affected to a greater degree than men. Treatment is either by pinning or by arthroplasty. Total hip replacement arthroplasty is being increasingly used in the elderly because of the shorter convalescence and decreased mortality, even so mortality is still considerable.

Fracture of the Wrist

Colles' fractures are commonly associated with osteoporosis. This fracture is generally caused by falls on the outstretched hand and involves the distal radius and the styloid process of the ulna. The result is the classic 'dinner fork' or 'silver fork' deformity of Colles' fracture, so called because of its resemblance to a fork in profile. The mean age of affected women is about 60 years and at least 90 per cent of them are postmenopausal, many of them very close to the menopause (Nordin *et al*, 1984). The occurrence of a Colles' fracture is often taken to be an early indication of osteoporosis.



N=Normal; EP=End Plate Collapse; W=Wedging; C=Crush.

Source Adapted from Woolf *et al*, 1988.

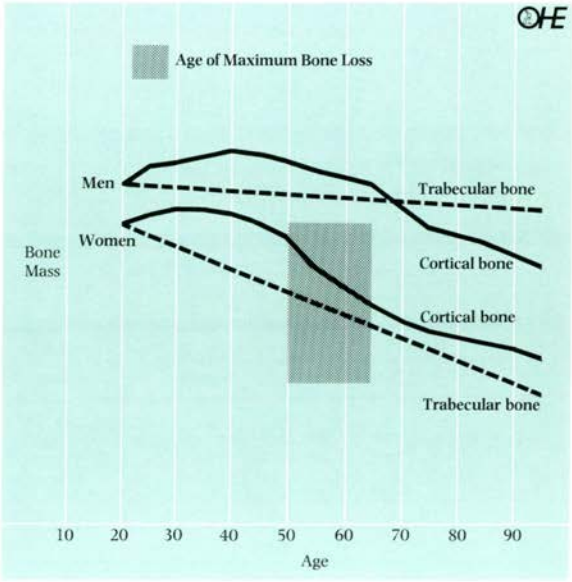
Fracture of the Vertebra

Vertebral fractures become more frequent from approximately age 50, particularly in women. These fractures can be divided into two groups: wedge fractures; and crush fractures. They vary in both severity and pain. The process known as 'permanent vertebral deforming events' occurs in up to three stages (see Figure). At stage one there is increased bioconcavity of the vertebral bodies often with loss of height, stage two is the wedged vertebral body and stage three complete vertebral body crush. A single vertebral fracture of the wedge type may be simply a result of trauma, but if two or more vertebrae are affected, especially if crushed, the condition is likely to be due to trabecular osteoporosis.

growth spurts which occur during adolescence are a result of the formation of new bone on both the outer and inner surfaces of existing bone. Although this process eventually slows this is the pattern of bone formation which continues into adulthood. During the third phase, the two processes of formation and resorption are closely balanced and it is therefore necessary to maintain bone supply. This is chiefly done by ensuring that there is sufficient calcium in the diet and by taking regular exercise (Editorial *Brit Med J*, 1987). The fourth phase is one of net bone loss. The rate of breakdown exceeds that of new formation, and bone mass begins to decline.

Regardless of race or sex everybody loses bone with age, the difference is the amount and the rate of loss. Peak bone mass for both sexes is reached during the early twenties (Notelovitz *et al*, 1982) at which point the cells begin to uncouple and the activity of osteoclasts exceeds that of osteoblasts leading to loss in bone mass (Riggs and Melton, 1986). The

Figure 3 **Bone loss with age: a comparison of men and women**



Source Redrawn from Notelovitz *et al* (1982)

peak bone mass of men is higher than women and in addition women lose bone mineral density at a faster rate than men (see Figure 3). Bone loss in men occurs at 0.4 per cent per annum beginning at age 50 and does not generally present a problem until the age of 80. In women bone loss begins at round age 30 at a rate of 0.75 to 1 per cent a year. The onset of the menopause in some women may cause the rate of bone mineral loss to accelerate to between 2 and 3 per cent until five years after menopause. At this rate a woman may have lost a third of her bone mineral mass by the age of 70 (Smith, 1987). It has been suggested that bone mineral mass is directly related to bone strength (Wilson, 1985). Thus decreased bone mineral content results in increased susceptibility to fracture.

Although all bones undergo age related changes they are not all affected in the same way. The differences are due to the structural make up of the two basic kinds of bone tissue. The first is cortical bone which looks solid and dense, the second type is trabecular bone, which is more porous. The relative proportions of each differ from one bone to another and even within parts of a particular bone. Cortical bone constitutes 80 per cent of total skeletal mass and predominates in the shafts of the long bones, whereas trabecular bone is concentrated in the vertebrae, the pelvis and other flat bones and in the ends of long bones.

Despite its delicate appearance, trabecular bone is very strong, its lattice-like structure provides maximum support with the minimum of material. But because of this structure it has a large surface area and therefore bone loss can occur there (Smith, 1987). For this reason those bones which have high concentrations of trabecular bone, for example the vertebrae, are particularly vulnerable to disturbances in the bone remodelling process. Women lose about 35 per cent of their cortical bone and 50 per cent of their trabecular bone during their lifetime, while men only lose about two-thirds of these amounts (Riggs and Melton, 1986).

What is osteoporosis?

Osteoporosis is the most common disorder of the skeleton. It is characterised by a reduction in both the amount and strength of bone tissue sufficient to result in the affected part or parts of the skeleton being abnormally susceptible to fracture. It is generally held that the chemical composition of the bone in osteoporosis is no different from normal bone; there is simply less of it (Nordin, 1983). This makes osteoporosis different from other bone diseases, most of which are associated with abnormal bone composition. For example, with osteomalacia, the adult equivalent of rickets, there is a deficiency of calcium phosphate crystals in the bone matrix.

To define osteoporosis further is difficult in that for any specific age and sex there is a wide and continuously distributed range of bone mass and no distinctly separate group who can be described as having low

bone mass. As previously stated bone mass begins to decline from around age 30 in women and age 50 in men (Smith, 1987). Therefore low bone mass is nearly universal among the very elderly. At present there is no generally agreed biological definition of a level of bone loss which can be used to confirm the presence of osteoporosis.

Types of osteoporosis

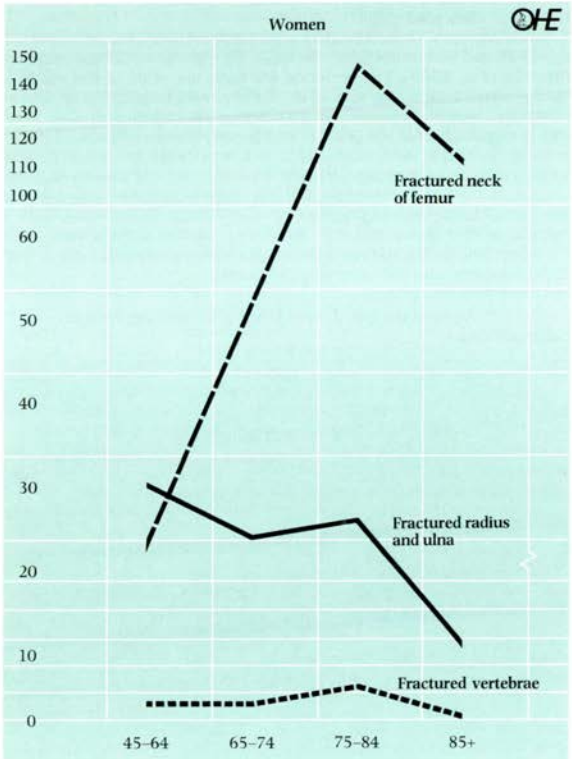
Osteoporosis is usually divided into two types: primary and secondary osteoporosis. Secondary osteoporosis can often be attributed to a single cause, either a disease or a drug, and can occur in both sexes and in children as well as adults. Within primary osteoporosis two phases of bone loss have been identified affecting both cortical and trabecular bone (Riggs and Melton, 1983). A protracted slow phase which occurs in both sexes which is commensurate with age (senile osteoporosis) and a transient accelerated phase which occurs in women after the menopause, bone loss being in excess of that expected with age (postmenopausal osteoporosis).

The slow and accelerated phases of bone loss are associated with two different abnormalities of bone remodelling. The slow, age dependent phase is on the whole a consequence of impaired bone formation; the osteoclasts resorb bone at a normal rate but the activity of the osteoblasts is impaired leading to reduced bone formation. In postmenopausal osteoporosis, there are more osteoclasts resorbing bone and the osteoblasts are unable to form bone at the same rate resulting in bone loss.

Differences in the rate and timing of cortical and trabecular bone loss explain the fracture patterns which occur (Nordin *et al*, 1984). The incidence of Colles' fractures (distal forearm) and of vertebral fractures increases soon after the menopause (see Figure 4(a) and (b)). The incidence of Colles' fractures continues to rise until the age of 65 and then reaches a plateau, whereas the incidence of vertebral fractures continues to rise steadily beyond that age. These two types of fractures occur at sites with large amounts of trabecular bone (Aitken, 1984). The incidence of hip fractures, however, slowly increases with age until approximately age 70 when the incidence of fracture increases dramatically (see Figure 3). The hip contains substantial amounts of both cortical and trabecular bone which explains why such fractures occur later in life, but not the increase in incidence, which can only be explained in part by a longer life expectancy.

Postmenopausal osteoporosis is characterised by vertebral and Colles' fractures (Riggs and Melton, 1986). The vertebral fractures are generally the 'crush' type (Nordin *et al*, 1984). With postmenopausal osteoporosis the rate of trabecular bone loss can be up to three times higher than the norm whereas the rate of cortical bone loss is only slightly higher (Riggs and Melton, 1986). Two main factors determine a woman's susceptibility to postmenopausal osteoporosis (Stevenson *et al*, 1989): firstly, the peak bone mass attained, as influenced by sex, race, nutrition and physical activity (*Drugs and Therapeutic Bulletin*, 1989), secondly, the subsequent bone loss. A primary cause of bone loss is the decline of ovarian function and of the reduced production of oestrogen associated

Figure 4a Age and sex specific incidence of various age related fractures – women

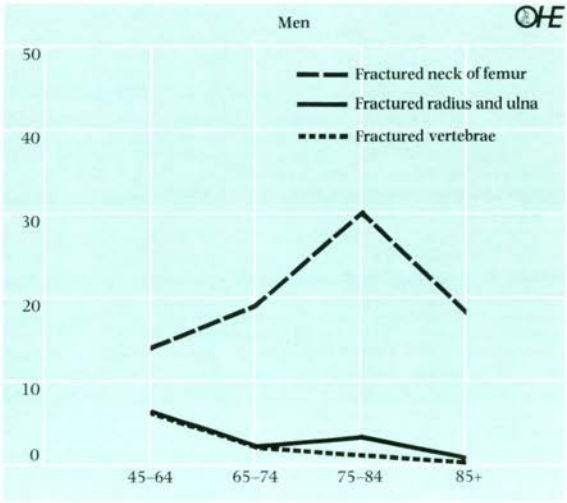


Source HIPE.

with the menopause. But all women are oestrogen deficient after menc pause (Nordin, 1983) yet not all of them develop postmenopausal ostec porosis, thus other factors must interact with this deficiency to deter mine individual susceptibility.

Senile osteoporosis occurs in both men and women generally over th age of 70 and is manifested in the main by hip and vertebral fracture (Resnick *et al*, 1989). The vertebral fractures are often of the multipl 'wedge' type, which may lead to dorsal kyphosis, commonly known a 'dowagers hump'. The trabecular thinning associated with slow bon loss is responsible for the gradual and usually painless vertebral defor mation. In those individuals with senile osteoporosis bone densit measurements at clinically relevant fracture sites are usually, but nc always, in the lower part of the normal range adjusted for age and sex but not all those who experience an osteoporotic fracture will have bone density measurement in the lower part of the normal rang Clearly other factors, such as an individuals propensity to fall play a par in determining who will experience a fracture.

Figure 4b **Age and sex specific incidence of various age related fractures – men**



Secondary causes of osteoporosis include: immobilisation and disuse, thyrotoxicosis, hypogonadism and Cushing's syndrome. Localised or generalised immobility rapidly produces osteoporosis (Smith, 1977). The damaging effects of bed rest on the skeleton have been recognised for some time and dual photon absorptiometry has been used to confirm the loss of vertebral bone in patients confined to bed (Krolner and Toft, 1983).

Thyrotoxicosis increases both the activity of osteoclasts (bone resorption) and osteoblasts (bone formation), but the activity of the osteoclasts is predominant and thus bone mass is reduced. Thyrotoxicosis is now quite rare due to early diagnosis and treatment, but when it does occur to a degree sufficient to cause osteoporosis it is primarily the cortical bone which is most affected (Woolf *et al*, 1988).

Hypogonadism in young men is a well known cause of osteoporosis. Bone resorption is increased with low bone formation. Patients are tall with long limbs, high pitched voices and feminine distribution of fat and hair.

Cushing's syndrome due to adrenal cortical over activity is rare; but iatrogenic disorder as a result of prolonged use of corticosteroids is more common. Both may cause severe osteoporosis. The extent to which bone mass is lost through reduced osteoblast activity is dependent on how long and in what dose the corticosteroids are taken. But instances of spontaneous fracture have been reported within weeks of commencing corticosteroids. Trabecular bone is primarily affected especially in the vertebrae.

Low bone mass has been found in women athletes with premenopausal hypothalamic amenorrhoea (absence of menstrual flow) and a reduction in radial bone density has also been recorded in women with anorexia nervosa and vertebral fractures may occur (Cummings *et al*, 1985). In such women osteoporosis is thought to be related to the low mean oestrogen concentrations (Smith, 1987). Similar oestrogen deficiency probably contributes to the stress fractures incurred by young ballet dancers; their frequency is due to the delay in the menarche and the incidence and duration of secondary amenorrhoea (Woolf *et al*, 1988).

Epidemiology of osteoporosis

The epidemiology of osteoporosis presents particular problems since it is not a condition which on its own causes complaint. People with osteoporosis do not come to the attention of the medical profession until something has happened, usually a fracture but also loss of height or back pain. Since there is no single necessary and exclusive attribute of osteoporosis by which it can be estimated, recognition of the condition and therefore estimates of its prevalence depend on the standpoint of the observer.

There are three different approaches to estimating the number of people in the population with osteoporosis. Firstly, the perceived prevalence, that is the number of times doctors make the diagnosis; secondly,

the clinical prevalence, that is the number of times osteoporosis related conditions bring patients to medical attention regardless of whether the condition is recognised. This figure may be up to twenty times higher than that for perceived prevalence since it will include the majority of the fractures of the wrist, humerus and femoral neck that occur; thirdly, the biological prevalence, the number of patients who have a pathological degree of osteoporosis (as judged by age, sex and race) whether or not the condition has led to a clinical disease.

Two further factors complicate the process of assessing the prevalence of osteoporosis. Firstly, its clinical condition generally presents as a fracture, which is an all or nothing phenomena, either a subject has a fracture or does not. Fractures occur in a variety of circumstances, for example, slipping in icy conditions and the occurence of such accidents would obviously distort the 'perceived incidence' of osteoporosis in northern as compared with tropical countries (Woolf *et al*, 1988).

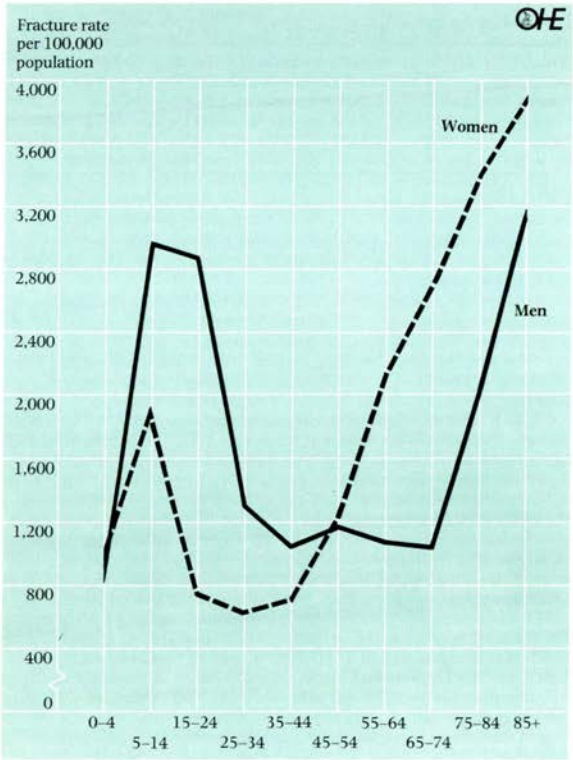
Secondly at present the biological prevalence of osteoporosis can only be measured by methods that assess bone density and it is unsafe to assume that bone density will bear a close and constant relationship to bone strength. Whilst this assumption appears to be confirmed for vertebral fractures in that researchers have consistently found less trabecular bone on average in women with vertebral fractures than in women of similar age without vertebral fractures the relationship between bone density and hip and Colles' fractures is less clear. Case control studies have also consistently found lower average cortical and trabecular bone mass in patients with hip fractures than in controls of similar age. However, there is a wide overlap between fracture cases and controls (Aitken, 1984; Riggs, 1988; Cummings, 1985). This finding indicates that although a reduction in spinal bone mass is the primary determinant of vertebral fractures, other factors in addition to low bone mass (which is virtually universal among the very elderly) are important in determining who will suffer a hip or Colles' fracture.

Nevertheless, as an indicator of the prevalence of osteoporosis it is the clinical condition, that is the number of people who come to medical attention for osteoporosis related conditions regardless of whether or not the connection is made, which is of primary importance to health care planners since it is on these figures that the need for health care resources will be determined. Thus the most usual expression of osteoporosis is the increased liability to fracture, particularly the hip, vertebrae and wrist. For this reason emphasis has been placed on the relationship between the incidence of fractures and age, sex and race.

Fractures are common, particularly among the young and the very old. Figure 5 shows the pattern that is characteristic of the age distribution of limb fractures. The distribution of fractures is bimodal, there is a peak in youth (usually male and associated with trauma) which then declines, the incidence again rises in those over 50 years of age and continues to rise. In 1985 alone nearly 1 per cent of women aged over 75 in England sustained a fracture of the hip (Hospital In-Patient Enquiry (HIPE), 1985). The location of the fractures and the level of trauma involved are quite different at the two extremes of age.

Fractures among children and young adults are related to substantial

Figure 5 **Age and sex specific incidence of limb fractures in Rochester, Minnesota 1969–71**



Source Redrawn from Melton and Riggs (1987).

trauma, usually a result of sporting injuries or road traffic accidents and are more common in boys than girls. These fractures involve the shaft of the long bones of the extremities and primarily consist of cortical bone. In contrast, the fractures which are related to ageing and therefore osteoporosis have three distinct features, the incidence rates are higher

Table 1 **Distribution of fractured neck of femur cases by age and sex: England 1985**

	Number of cases by age (% of total)					
	0–44	*45–64*	*65–74*	*75–84*	*85+*	*All ages*
Male	1,330 (3)	1,370 (3)	1,890 (4)	3,010 (7)	1,840 (4)	9,440 (22)
Female	600 (1)	2,240 (5)	5,330 (12)	14,310 (33)	11,260 (26)	33,790 (78)
Total	1980 (5)	3,610 (8)	7,220 (17)	17,320 (40)	13,100 (30)	43,230 (100)

Source HIPE.

among women than men: the rates increase dramatically with age; and the fractures occur at sites with large proportions of trabecular bone (Melton *et al*, 1987).

The main age related fractures and those traditionally associated with osteoporosis are fractures of the distal forearm (Colles' fracture), vertebrae and hip. With sufficient force, these fractures can occur in anyone but they are described as being osteoporotic when they occur in the elderly or as a result of minimal trauma, that is as a consequence of a fall from no more than standing height (Cummings *et al*, 1985).

Colles' fractures are the most common fractures among women, until the age of 70 when their frequency is surpassed by fractures of the hip. At the time of the menopause, approximately age 45 to 50, there is a rapid increase in the number of fractures of the wrist but there is no significant increase among men of the same age (Figure 4(a) and (b)). Vertebral fractures become more frequent after the age of 50 particularly among women. Nordin (1983) suggests that 60 per cent of elderly women will experience vertebral wedging, 21 per cent a complete crush fracture and 10 per cent two or more crush fractures. This latter group have low bone mass, particularly of the lumbar vertebrae.

The incidence of fractures of the hip increases rapidly after the age of 70 (Table 1). Approximately 80 per cent of all cases of hip fracture occur in women over the age of 45. Using current age and sex specific incidence rates for England and Wales the probability of a woman suffering a fractured hip before the age of 85 is 12 per cent compared with only five per cent for men (Royal College of Physicians, 1989).

Although these three fractures are interrelated, in that patients who have sustained one have an increased risk of sustaining another at a different site (Woolf *et al*, 1988), the correlation is less well marked than one might expect if they were all a consequence of a generalised reduction in bone mass. The difference is probably due to the balance of cortical and trabecular bone at the various sites and their differential loss with ageing (Riggs, 1988) and or the variable and unpredictable role of trauma.

Vertebral wedging and crush fractures lead to loss of height and occasionally severe pain but these fractures rarely require much medical care or hospitalisation. Colles' fractures can cause disability until

healed but it is fractures of the hip which have the largest medical and social impact, needing hospitalisation and frequently surgery. Also many of these patients do not return to their previous environment.

It has been calculated that fractures of the hip are associated with more deaths, disability, and medical costs than all other osteoporotic fractures combined. In 1985 in England there were 43,230 fractures of the hip. Clearly as the number of elderly increases the number of hip fractures will also increase. However, this does not fully explain the large increase in the age-adjusted incidence in the 20 years prior to 1978 (Fenton Lewis, 1981).

Various hypotheses have been put forward to explain this large increase in incidence. It has been suggested that in the United Kingdom the group of people at risk lived on a fixed income (old age pension) at a time of high inflation in the early to mid 1970s and probably adjusted their diets accordingly, also poor diets during and between the wars (Wallace, 1983) might be in part responsible. Other theories which have more credence include the decrease in mobility associated with a more sedentary lifestyle and the increased use of transport and the prevalence of smoking in the first half of this century. The report of the Royal College of Physicians states that there is likely to be an interval of 50–60 years between the start of smoking and experiencing a fracture.

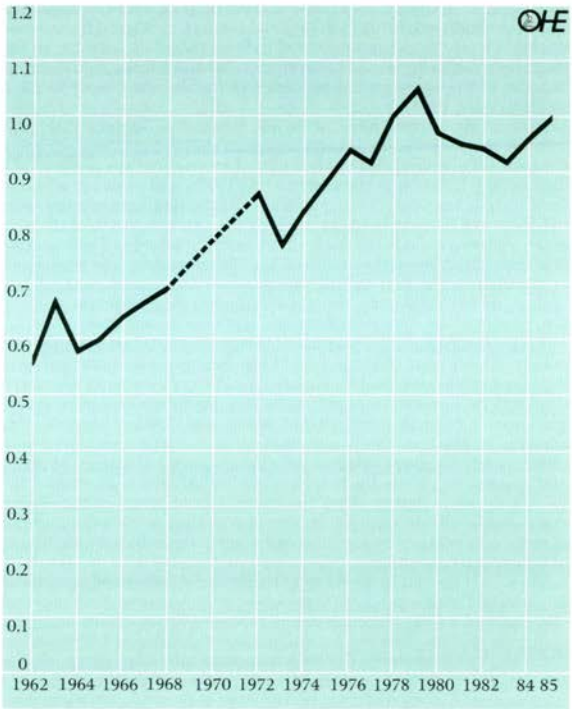
Baron (1987) suggested that smoking was associated with an approximately 50 per cent increase risk of hip fracture and a 400 per cent increased risk in vertebral fracture in the elderly. Bone density has been shown to be lower in men and post-menopausal women who smoke than non-smokers (Daniell, 1976; Seeman *et al*, 1983). However, after allowing for the lower body weight of smokers (factors associated with obesity protect against osteoporosis) the association between smoking and increase risk of hip fractures has not been shown in all studies. But there is no doubt that smoking has an effect, but how much the effect is due to reduced body weight and other factors such as the increased rate of metabolism caused by smoking on endogenous oestrogen activity and of Vitamin D is uncertain.

Since 1978, as can be seen from Figures 6 and 7 the incidence rate in England and Wales per 10,000 population for fractured neck of femur has declined (HIPE) although the numbers of hip fractures occurring continues to rise. Reasons for the apparent decline in incidence are unknown but it is possible that rationing during the War, which affected the entire population, resulted in a uniformly well-balanced diet at a time when the women of seventy-five years and over in 1978 and up to the present were between 30 and 40 years old and had just attained or were attaining peak bone mass.

The consequences of hip fracture are often severe. The average length of stay in hospital was 29.8 days in 1985 (HIPE) and in the first year after fracture the mortality rate in patients with a fractured hip is approximately 20 per cent higher than in persons of a similar age and sex who have not sustained a fracture (Fenton Lewis, 1981). Most of the excess mortality occurs in the first four months after the fracture. Advanced age as well as pre-existing illnesses, disablity and institutionalisation increase the risk of dying after the fracture (Cummings, 1985).

Figure 6 **Hospital in-patient admissions for fractured neck of femur in men over 65 years of age**

Index 1985 = 1.0

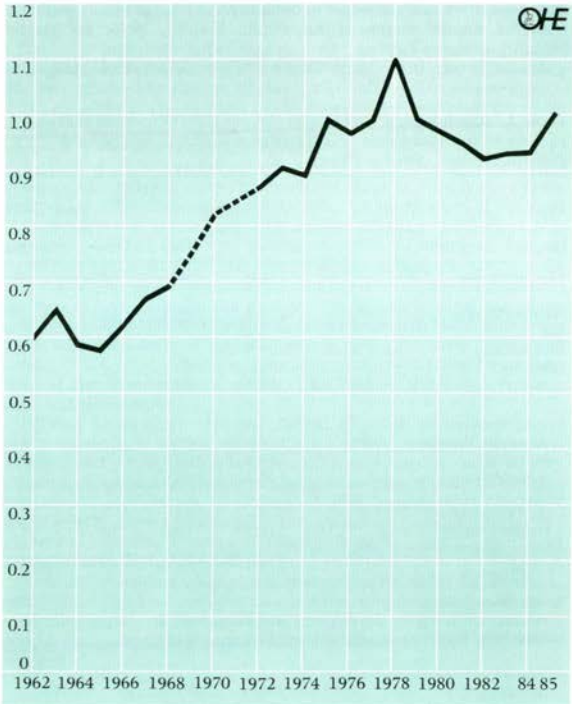


*Age adjusted admissions index calculated by applying hospital in-patient admissions by patient age in ten year groups in the base year of 1985 to the population at risk in other years.

Sources HIPE and OPCS (for years quoted).

Figure 7 **Hospital in-patient admissions for fractured neck of femur in women over 65 years of age**

Index 1985 = 1.0



*Age adjusted admissions index calculated by applying hospital in-patient admissions by patient age in ten year groups in the base year of 1985 to the population at risk in other years.

Sources HIPE and OPCS (for years quoted)

Those who survive fracture of the hip often suffer permanent disability and dependency, many who were previously independent are obliged to remain in long-term care. Those who return home are often dependent upon other people for mobility. Loss of function and independence are most likely to occur in patients who have previous history of impaired mental status or functional disability prior to fracture (Wootton *et al*, 1982).

As can be seen from Figure 4(a) and (b) the incidence of osteoporotic

Table 2 **Age-adjusted* incidence rates per 100,000 person years for various limb fracture sites in different population groups among persons 35 years of age or older**

	Proximal Femur		*Distal Forearm or Colles'*	
Geographic Locality	*Women*	*Men*	*Women*	*Men*
USA, Rochester	295.0	126.9	396.4	86.0
Sweden, Malmo	203.2	88.3	332.1	49.5
New Zealand				
Whites	178.3	80.9		
Maori	88.3	70.9		
Israel, Jerusalem				
American/European	174.6	97.2		
Native born	145.8	92.5		
Asian/African	126.4	98.4		
United Kingdom				
Oxford/Dundee	114.9	59.2	304.4	72.9
Finland	114.1	64.4		
South Africa, Jo'burg				
Whites	217.3	83.2		
Bantu	12.4	12.6		
Singapore			58.3	61.6
Indian	268.0	117.7		
Chinese	50.3	90.9		
Malay	20.3	33.0		
Hong Kong	72.4	63.4		
Yugoslavia				
High calcium	39.7	42.3	221.3	98.1
Low calcium	91.5	88.4	196.9	112.2

*Age-adjusted to total 1970 United States whites.

Source Adapted from Melton and Riggs (1987).

fractures is much lower among men than women although the degree of female predominace depends on the type of fracture. The age-specific incidence rates of hip fractures among women is approximately two to three times higher than among men, and for Colles' fractures the incidence is between six and eight times higher for women (Cummings *et al*, 1985).

The frequency with which age related fractures occur in different geographic areas varies considerably. Whilst part of the discrepancy may be explained by the use of non-comparable definitions or incomplete case ascertainment much of the geographical variation may well be real. Fracture rates appear to be higher in temperate countries, for example, in Sweden (Table 2) the incidence of hip fractures are very high. However, this does not appear to be as a direct result of the severe weather conditions since most hip fractures occur indoors. A more likely explanation of the difference is the fact that incidence rates of fractures seem to be higher among whites than non-whites regardless of geographical area, thus indicating that the variation is more closely related to race (Melton *et al*, 1987). The reasons for the differences between the races are largely unknown, although studies have shown substantially greater levels of bone density in American blacks than whites of the same age and sex. But the Bantu who, as can be seen in Table 2, have the lowest incidence rates of hip fractures of any population have been found to have values of metacarpal bone desity which are lower than those of the Johannesburg whites, who display the usual Western pattern of hip fracture.

Diet may be an alternative explanation, although available information is not entirely consistent. Matkovic's (1979) study in Yugoslavia demonstrated a relationship between calcium intake and bone density in two rural populations, however, there were other dietary differences between the populations. In addition it often appears that groups of people which seem to have poor diets, such as the Bantu, that are deficient in calcium, protein and vitamin D, have lower fracture rates than areas with 'better' diets (Melton *et al*, 1987).

Much of the epidemiological documentation on racial differences is weak and few studies have been based on the comprehensive evaluation of fractures in patients and appropriate controls from the different racial groups. Thus convincing explanations for apparent racial differences are awaited.

Socio-economic cost of osteoporosis

Osteoporotic fractures in the elderly present a major health care and social problem which is largely preventable. The consequences of these fractures are enormous both socio-economically and as regards morbidity and mortality.

Vertebral fractures lead to loss of height and can cause severe pain and discomfort but they generally do not call for much medical care or lengthy periods in hospital. Such fractures can be categorised as 'wedge fractures', the deformity of the anterior portion of the vertebra or as

'crush fractures' which affect the entire vertebra. In Denmark (Jensen *et al.* 1982), approximately 5 per cent of 70 year old women have crush fractures of at least one vertebra and in Rochester, USA, about 40 per cent of white women have at least one wedge fracture by age 80 (Cummings *et al.* 1986). Since fractured vertebrae never regain their normal shape, multiple fractures may lead to a kyphotic posture, dowager's hump, loss of height and sometimes acute back pain and functional limitations. Approximately two million women suffer from osteoporosis losing up to ten inches in height and suffering pain in their back and ribcage because of gradual vertebral collapse.

Colles' fractures are rarely fatal but can cause considerable disability until mended. Most patients recover function without the use of rehabilative services although many may require temporary support from others.

It is again stressed that fractures of the neck of femur (hip) have the greatest impact of all osteoporotic fractures both socially and economically. Hip fractures produce substantial mortality and disability, the vast proportion of such fractures occurring in the 65 and over age group. Whilst it appears that the incidence rate in England and Wales per 10,000 population for fractured neck of femur is declining (see Figures 6 and 7) the fact still remains that the number of hip fractures is continuing to rise because the size of the population over the age of 65 is increasing. Data from HIPE indicate that in 1985 of a total number of fractured neck of femur cases of 43,230 in England (strictly discharges or deaths in hospital), 87 per cent (37,640) occurred in the 65 years and over grouping and 71 per cent (30,900) of the total number of cases occurred in women over the age of 65 (see Table 1). This compares with a total number of cases of fractured neck of femur in the 65 years and over grouping in 1965 in England of 15,726 of which 81 per cent (12,737) occurred in women in the same age group.

Several studies concentrating on fractured neck of femur have noted that the number of cases of fractured neck of femur amongst the over 65's has more than doubled and from this fact have made the assumption that the pattern will be repeated in future years. However, as can be seen from Figures 6 and 7 a standardised admissions ratio indicates that following a peak in incidence rates in 1978/79 incidence rates would appear to have begun to fall. This does not mean that the total number of cases of fractured neck of femur is declining, but simply that the number is not increasing in excess of the increase in population.

Those who experience fractures of the hip are usually those people who are just managing to remain independent and self-sufficient. Such a fracture not only requires lengthy hospitalisation and often surgery but also many of those who fracture cannot return to their previous environment thus placing the full burden of their care onto their relatives or the community.

At least half of those able to walk before sustaining a hip fracture cannot walk independently after (Miller, 1978). The ability of such patients to care for themselves is greatly reduced and hip fractures are often the event which precipitates institutionalisation. In one study, conducted in the United States, it was found that as many as 8 per cent of all nursing

Table 3 **Mean duration of stay in hospital for fractured neck of femur by age and sex; England and Wales, 1985**

	Age (years)							
	0–4	*5–14*	*15–44*	*45–64*	*65–74*	*75–84*	*85+*	*All ages*
Male	15.5	33.4	30.2	21.0	24.9	34.7	31.3	29.4
Female	31.3	18.6	22.2	20.2	23.6	29.9	34.9	29.8

Source HIPE.

Table 4 **Mean duration of stay in hospital for fractured neck of femur by age and sex; England and Wales, 1965**

	0–4	*5–14*	*15–19*	*20–24*	*25–34*	*35–44*	*45–64*	*65+*	*All ages*
Male	32.4	33.7	38.9	26.5	35.9	36.3	29.0	51.8	44.2
Female	44.0	34.9	43.3	62.0	42.3	42.1	40.1	53.3	51.3

Source HIPE.

Table 5 **Mean duration of stay by Regional Health Authority for fractured neck of femur, England and Wales, 1985**

Region/Country	*Mean Duration of Stay*
England and Wales	29.7
England	29.8
Northern	28.9
Yorkshire	31.4
Trent	30.7
East Anglia	31.2
North West Thames	32.5
North East Thames	31.7
South East Thames	21.5
South West Thames	33.0
Wessex	24.6
Oxford	24.0
South Western	22.7
West Midlands	35.8
Mersey	33.1
North Western	31.3
Wales	20.9

Source HIPE.

home residents had experienced a hip fracture (Holbrook *et al*, 1984). In England there are 259,849 persons aged 65 and over resident in non-private households, which include local authority, private and voluntary homes and psycho-geriatric wards both within and outside the NHS (1981 Census) but no figures exist to indicate how many of these residents have experienced hip fractures.

Fracture of neck of femur has significant resource implications for the NHS, particularly the hospital sector. In 1985 there were 43,230 hospital admissions for fractured neck of femur in England (HIPE). This figure represents 0.85 per cent of admissions for all causes but rises to 2.2 per cent in the over 65 age group and accounts for 3.4 per cent of all female admissions in this age group.

On average, hip fracture patients spend 29.8 days (Table 3, HIPE) as hospital in-patients, yielding a total of 1.29 million bed days in England in 1985. There has been a reduction in the length of time spent in hospital for hip fracture. In 1965 the mean duration of stay as hospital in-patients for hip fracture was 44.2 days for men and 51.3 days for women (Table 4, HIPE). There are considerable differences in mean duration of stay between regional health authorities in England and Wales (Table 5, HIPE). For example, in West Midlands Regional Health Authority the mean duration of stay as hospital in-patients was 35.8 days in 1985 as compared with 21.3 days in South East Thames Regional Health Authority.

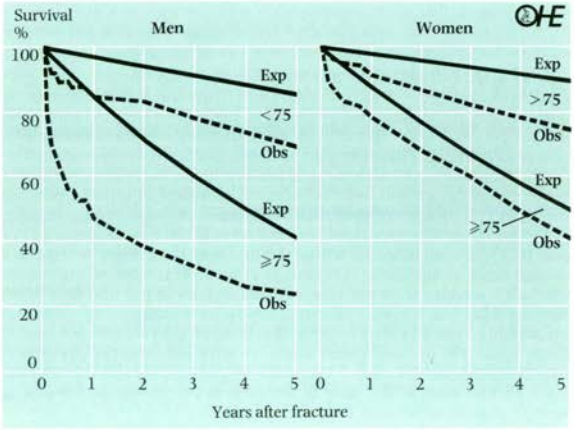
In 1985/86 the average cost per day in large acute hospitals was £95 so that the annual cost of fractured neck of femur for that year may be calculated to have cost £122.5 million, £87.5 million of which was spent on women in the over 65 age group. Uprating on a *pro rata* basis to

include Wales increases this sum to £128 million and £92.7 million respectively. In the United Kingdom it has been estimated that direct hospital costs of hip fracture are in the region of £160 million per year (1987/88 prices, DHSS estimates, Royal College of Physicians, 1989).

It should be noted that these figures are an understatement of the actual costs of hip fracture since they do not include the costs of out-patient appointments, community nursing and social services for hip fracture patients nor the costs of a reduced quality of life for both the patient and their relatives.

The Royal College of Physicians in their report on fractured neck of femur found that there was a real need to improve the treatment of hip fracture not only in order to improve the survival and quality of life of patients following hospital treatment but also to ensure the effective use of hospital resources. In an analysis of the stages of care during hospital stay for hip fracture it was found that 10 per cent of bed days were spent awaiting a theatre session, 51 per cent recovering from surgery without complications and 28 per cent waiting to leave the orthopaedic ward despite being declared medically and surgically fit to do so (Report of a Working Party to the Secretary of State for Social Services, 1981). This latter figure indicates an inadequate provision of places for nursing care

Figure 8 **Observed (Obs) and Expected (Exp) survival for Rochester, USA, residents following proximal femur fracture at ages under 75 years or 75 years and over.**



Source Redrawn from Melton (1988).

Table 6 **Fractured neck of femur – deaths: mentioned and inferred, 1985**

Age at Death (years)	*Male*	*Female*
0– 4		
5– 9		
10–14		
15–19	1	
20–24		
25–29		
30–34		
35–39	2	
40–44	2	
45–49	2	1
50–54	1	4
55–59	6	9
60–64	14	11
65–69	25	55
70–74	65	103
75–79	141	327
80–84	181	565
85–89	161	688
90–94	77	387
95+	28	145
All ages	706	2,295

Source OPCS 1985.

outside acute hospital beds. It is wasteful of resources since acute surgical beds cost more than geriatric beds. Thus the factors prolonging hospital stay were not directly related to medical or surgical care, if all the patients had been operated on without delay and if immediate discharge or transfer of patients who no longer needed to be in acute orthopaedic wards for medical or surgical reasons had occurred over a third of hospital bed days could have been saved. In financial terms a possible saving in 1985 of approximately £43 million.

Among those who experience hip fractures in the United States, 12 per cent to 20 per cent more die within the first year than might be expected on the basis of age alone (Cummings *et al*, 1985), most of this excess mortality, which varies with age and sex, occurs in the first four to six months after the fracture (Melton, 1988). In a study of hip fractures on patients from an entire community, it was found that 90 per cent of those under the age of 75 were still alive after one year (92 per cent of expected) compared to only 73 per cent (83 per cent of expected) of those aged 75 and over at the time of fracture. Survival was better among women than men (Melton, 1988) (see Figure 8).

In England and Wales hip fractures are associated with many deaths. In 1985 there were 2,295 deaths from fractured neck of femur among

women and 706 deaths among men of all ages (Table 6, OPCS), but it is difficult to estimate the relative contribution of hip fracture to mortality since hip fractures can in themselves be seen as an indicator of poor health. Hip fracture patients often have a variety of co-existing conditions such as poor balance and muscular weakness and the occurrence of a fracture often precipitates additional adverse events. For example: many of those who break their hip will have lain for some considerable time on the floor unattended following a fall. It has been found that the longer the period of time spent on the floor following a fall the greater the likelihood of developing pressure sores and pneumonia (Woolf *et al*, 1988); emergency surgery on these traditionally elderly patients may be associated with increased mortality (Melton, 1988); and the subsequent immobilisation in bed may be accompanied by additional risks of venous thrombosis and pulmonary embolism. However, the falls which usually precede a hip fracture do not seem to directly contribute to overall mortality since other osteoporotic fractures rarely result in death, except following severe trauma. Colles' fractures, for example, are associated with falls but are rarely associated with death.

Identification of risk

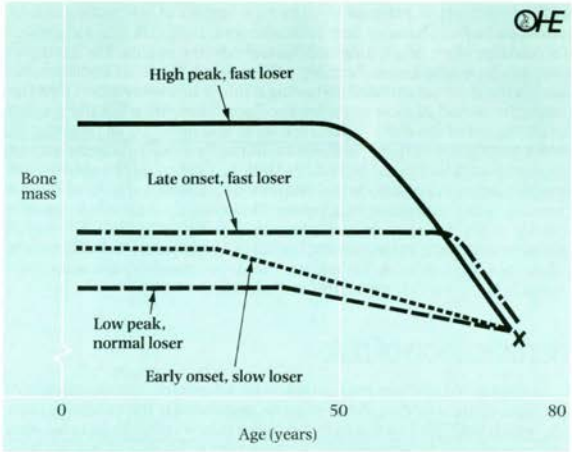
Some degree of bone loss is inevitable with advancing age irrespective of sex, race, climate or diet. What must be prevented is the excessive bone loss which may lead to fracture following minor trauma. In order that osteoporosis can be prevented it is necessary to be able to predict who will develop the condition. On the basis of past experience it is possible to predict that a proportion of a defined population will develop osteoporosis but it cannot be predicted with any degree of certainty for the individual. Practical measures to prevent osteoporosis depend on being able to identify those individuals or groups of individuals most at risk.

Theoretically, it should be possible to draw up a list of risk factors for osteoporosis and related fractures to quantify an individuals risk. However, despite better understanding of the risks no study has as yet developed an index to weigh these factors according to their importance in the development of osteoporosis. The factors that appear to be responsible for bone loss and that predispose towards osteoporotic fracture are basically the same as those which determine bone mass (Heaney, 1987), that is age and sex, genetic, mechanical and nutritional /hormonal factors.

Age and Sex

Ageing is one of the most important determinants of bone loss. By the age of 70 bone mass may have declined by 30 per cent or more in women, less in men, but there are many elderly people who do not show any marked difference in bone mass nor do they fracture their bones. It is generally accepted that a reduction in bone mass is a significant determinant of fracture. Therefore the peak bone mass attained at skeletal maturity, during the twenties, may in part explain why not all elderly people lose sufficient bone mass to fracture their bones, that is the

Diagram 1



Source Redrawn from Woolf *et al* (1988).

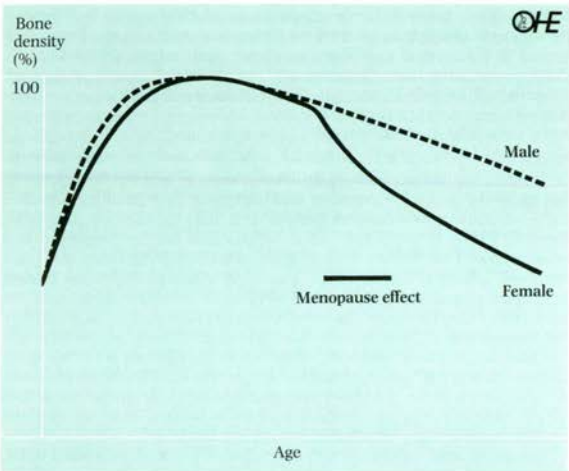
greater the peak bone mass the larger the amount of bone that can be lost before reaching the point where fractures are likely to occur (see Diagram 1).

Bone mass in men is greater than in women at all ages and at all skeletal sites and this difference increases after the menopause. It is the menopause which changes the relative risk of osteoporosis to the detriment of women more effectively than any other factor (Lindsay, 1987) (see Diagram 2).

Hormonal Factors

It was in 1940 when Fuller Albright first proposed that the loss of ovarian function was a factor in osteoporosis and age-related fractures in women, this theory has subsequently been supported. At the time of the menopause, and even more suddenly if premenopausal bilateral oophorectomy (removal by operation of both ovaries) is undertaken there is an acceleration of bone loss, the loss is more evident in trabecular bone than in cortical bone. This acceleration is a self-limiting process, superimposed on the hormonal decline in bone mass that occurs with age.

Diagram 2



Bone loss as a function of age in males and females. Bone density is in arbitary units and declines at an approximately equal rate (at least as a percentage of the original mass) in both males and females. Superimposition of the effect of the menopause upon this gradual age-related decline of mass accentuates the risk of osteoporotic fractures among women as much as 50 per cent of the total decline of mass with age may be related to loss of ovarian function.

Source Redrawn from Lindsay (In: *The Osteoporotic Syndrome*: Edition 1987).

Oestrogens tend to protect bone against the resorbing actions of the parathyroid hormone. The decline in oestrogen levels at the menopause, due to the virtual cessation of the hormonal activity of the ovaries is associated with a rise in bone resorption attributable to the increased sensitivity of the bone to these bone resorbing agents. The bone mass of women in their fifties who had a surgical menopause twenty years earlier is significantly lower than in age-matched controls who are still menstruating but it is similar to women in their seventies who also had the menopause twenty years earlier (Richelson *et al*, 1984).

Oestrogen therapy prevents the bone loss brought on by removal of the ovaries or the menopause. Ever since Fuller Albright proposed a relationship between oestrogen loss at menopause and bone loss oestrogen therapy has been used to prevent or treat postmenopausal osteoporosis. But it was not until the mid 1970s that the value of oestrogen therapy, in arresting progressive bone loss and reducing the number of osteoporotic fractures, could be established (Lindsay *et al*, 1976).

Oestrogen therapy after menopause works by restoring the calcium balance that protects the bones in the same way that the oestrogens produced by the ovaries before menopause acted. Oestrogens also ensure the efficient absorption of calcium through the intestines. They also appear to stimulate the production of calcitonin in the thyroid gland, which protects the bones from the demineralising effects of parathyroid hormone and inhibits bone resorption (Gennari *et al*, 1987).

Parity

Oestrogens are lifetime protectors of bone mass in women, in support of this claim the available evidence would suggest that childbearing does not predispose towards osteoporosis and may in fact be protective (Daniell, 1976). If the dietary intake of calcium during pregnancy has been sufficient for both mother and unborn child, pregnancy can have beneficial effects on bone mass. The high levels of oestrogen during pregnancy stimulates the activation of Vitamin D (this promotes calcium absorption) and increases the production of calcitonin (which inhibits bone breakdown). Progesterone also increases during pregnancy and this too has a bone conserving effect. Not enough research has been done to indicate whether or not the larger the number of pregnancies the greater the protection from osteoporosis. All that can be said is that the risk of developing osteoporosis is higher in women who have not had children than in those who have (Stevenson *et al*, 1989).

The use of oral contraceptives may also be protective of bone mass. There is evidence that women who have used oral contraceptives for long periods of time have denser bones than women who have not (Notelovitz *et al*, 1982). It has been suggested that the hormones in oral contraceptive preparations (oestrogen and progesterone) stimulate the release of calcitonin which inhibits bone breakdown.

Body Build

Obese postmenopausal women are less likely to develop osteoporosis or experience fractures than slim women. This is because obesity protects against postmenopausal bone loss by increasing the amount of biologically available oestrogen. After menopause most oestrogen is produced following the conversion of androstenedione to oestrone. This conversion occurs in the adipose (fat) cells, consequently obese women produce more oestrone than thin women (Kiel *et al*, 1987). Being overweight therefore reduces the risk of developing osteoporosis. However, because obese women are continuing to produce oestrogen but following the menopause they are no longer producing progesterone the risk of endometrial cancer (cancer of the lining of the uterus) is reputed to be higher (Notelovitz *et al*, 1982). Progesterone protects the uterus lining from oestrogen over stimulation.

Greater body weight places more stress on the bones. In response to increased weight loads the formation of new bone is stimulated to meet the greater stress (Cummings *et al*, 1985). It is also probable that well padded hips are less likely to fracture with a fall (Kiel *et al*, 1987).

Genetic Factors

Black people have a higher skeletal mass and a lower incidence of osteoporosis than whites. Studies conducted in the United States indicate that blacks have greater bone mass, greater bone density, thicker bone cortex and fewer vertebral fractures than whites (Cummings *et al*, 1985). Age-specific incidence rates of fractures are approximately twice as high in white women as in black women. The reasons for these differences are not clear but there seem to be several factors which may account for this. In addition to larger bones at skeletal maturity blacks tend to have larger muscles. Muscle mass and bone mass are closely related in that the larger the muscles the greater the stress on the bones and consequently the larger the bones (Notelovitz *et al*, 1982). Black women tend to lose bone at a slower rate than white women and this is probably due to hormonal differences. There is also evidence to suggest that blacks have higher levels of calcitonin and it has also been shown that white women tend to lose more calcium in their urine than black women. Men do not appear to exhibit this racial difference.

Family history of osteoporosis has been widely cited as an important risk factor of osteoporosis, but until recently there was little evidence to substantiate this claim. The importance of family history was partly based on myth and inferred from studies of bone mass in identical and non-identical twins, the results of which indicated that genetic factors may have an important role in determining bone mass. However, recently a study concluded that premenopausal daughters of women with postmenopausal osteoporosis had reduced bone mass in the lumbar spine and the hip and this reduction in bone mass also seemed to put them at increased risk of fracture (Seeman *et al*, 1989). Interestingly, the same study also suggested that postmenopausal osteoporosis may result in part from a relatively low peak bone mass in young adulthood rather than from excessive loss of bone.

Physical Activity

The effect of gravity and the tension of contracting muscles help to maintain a positive balance between bone formation and resorption (Steinberg, 1987). Exercise increases blood flow to bones thus bringing in necessary bone building nutrients, it also affects the body's hormonal control of bone remodelling, moving the balance which normally exists between formation and resorption in favour of formation. Physical exercise seems to have a beneficial influence on the growing skeleton by helping to maximise peak bone mass. Long bone responds to mechanical stress and the effects of bone loss in osteoporosis may even be partially reversed by physical training (Schapira, 1988).

In osteoporosis caused by immobilisation therapeutic exercise and physical activity tends to slow the loss of and may restore bone mass (Krolner *et al*, 1983). With advancing age muscle mass, bone mass and physical activity all decline. In postmenopausal women a reduction in physical activity may be a significant contributory factor in the development of osteoporosis. A more sedentary lifestyle and the widespread use of cars for transportation and other mechanised aids to modern living has reduced the need for physical exertion.

It has long been recognised that prolonged bed rest and immobility leads to decreased bone mass in both young and old. Patients confined to bed may lose up to 1 per cent of trabecular bone per week, cortical bone is lost at a somewhat slower rate (Rambaut *et al*, 1970), weight bearing bones being those most affected. Resumption of normal weight bearing activity gradually restores both types of bone.

Athletes appear to have wider bones and more cortical bone in limbs that are involved in their particular kind of activity than in age and sex matched controls. Studies of tennis players found that the density and thickness of bone were only greater than normal in their playing arms (Smith, 1982). Since bone mass appears to be increased specifically in areas exposed to skeletal forces physical activity should be directed to those areas particularly susceptible to fracture (Schapira, 1988), that is the spine, the wrist and the hip, in order to minimise or even prevent their occurrence.

A programme of dynamic loading exercises of the distal forearm (tension, torsion, compression and bending) applied three times a week for 5 months to 14 postmenopausal osteoporotic women aged 53–74 showed a 3.8 per cent increase in mean bone density. In the control group mean bone density decreased by 1.9 per cent. The increase in trabeculae and the interchange of the marrow adipose tissue to red marrow were attributed to exercise (Simkin *et al*; 1987). In addition, Paganini-Hill *et al* (1981) in a case control study based in a retirement community suggested that a high frequency of outdoor exercise protects against hip fractures.

However, hormonal status appears to be more important than exercise, in that young women who become amenorrheic as a result of extreme exercise have reduced density of trabecular bone in their spines but little or no loss of cortical bone as compared to normal menstruating female athletes. Among women who have amenorrhoea from other causes, those who exercise regularly have greater bone density than those who do not (Woolf *et al*, 1988). Exercise is an attractive method for attempting to prevent osteoporotic fractures. Improvement of general physical wellbeing and the social effects of this are desirable by-products of continuous physical activity. It is also possible but unproven, that regular exercise may prevent falls and or help protect against injury during falls by improving neuromuscular function (Larson *et al*, 1986).

Dietary Factors

The most obvious deficiency of the bones of an osteoporotic patient is calcium. Calcium balance is dependent upon dietary calcium intake, the amount of calcium absorbed by the intestine and the amount excreted from the body. With advancing age the intestine becomes less capable of absorbing calcium from the diet, this change is most likely due to an age related decline in the production of calcitriol, the hormone which normally stimulates calcium absorption in the intestine (Tsai *et al*, 1984). A decline in the level of oestrogen at the menopause also decreases the efficiency of calcium absorption (Heaney *et al*, 1978).

At the time of the menopause when women have a reduced ability to absorb calcium, dietary intake often decreases particularly in western

populations. Many women have low calcium intakes because they are deliberately trying to avoid high calorie dairy products, which are also a major source of dietary calcium. But the role of low calcium intake in causing bone loss in postmenopausal women is uncertain. Matkovic *et al.* (1979) reported that the population of a district of Yugoslavia where consumption of dairy products was high had a 50 per cent lower incidence of hip fractures and a slightly higher amounts of cortical bone at all ages than in the population of a comparable district where calcium intake was much lower. The study suggests that high calcium intake throughout life may affect peak cortical bone mass thus affecting the rate of hip fractures (the incidence of Colles' fractures did not differ in the two districts). The rate of subsequent bone loss was found to be similar in both the high and low calcium intake districts (see Figure 9).

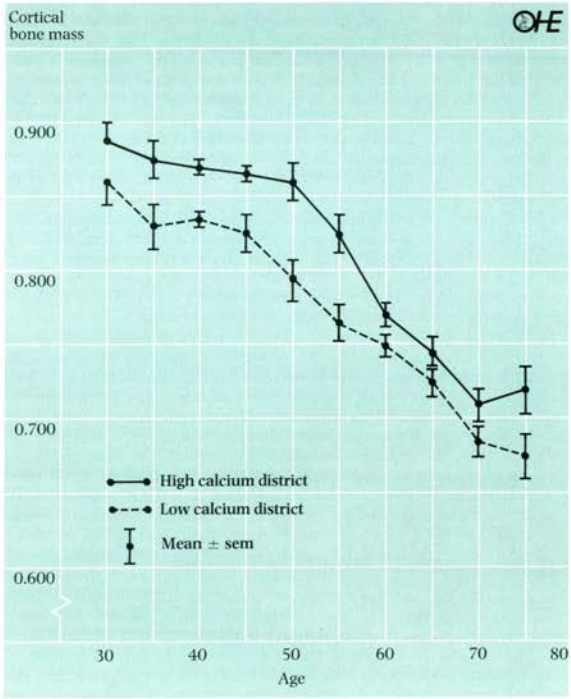
Two studies have suggested a positive effect of calcium supplementation on forearm bone mass in older women. In a short-term study by Jensen *et al* (1982) 500mg of calcium per day was found to arrest bone loss in 24 women aged 70 years. In a study by Smith *et al* (1981) bone mass increased in ten of 17 women (mean age 82 years) who completed three years of treatment with 750mg of calcium per day.

In a study of the effects of calcium supplementation on postmenopausal women, Riis *et al* (1987) concluded that 2,000mg of calcium per day slowed loss of cortical bone in the proximal forearm and total skeleton as compared with a group receiving a placebo but the rate of loss of trabecular bone in the distal forearm and spine was the same as in the placebo group. It was also found that calcium supplementation was not as effective as oestrogen and therefore could not be regarded as an effective alternative to HRT in the prevention of postmenopausal bone loss. A study by Riggs *et al* (1982) concluded that the postmenopausal fracture rate was improved by the use of calcium supplements and was also improved by oestrogen and fluoride treatment. When all three treatments were combined the fracture rate fell to a very low level.

Protein intake is also important. Excess dietary protein is metabolised and used immediately for energy or stored as fat. During the metabolising process there is an increase in urine calcium excretion. Normally an increase in protein intake is associated with an increase in phosphorus and phosphorus reduced urinary excretion of calcium. Unfortunately phosphorus also increases faecal loss of calcium. The net result of increased protein consumption remains a tendency toward more negative calcium balance.

The term vitamin D is used to describe the steroid hormones ergocalciferol and cholecalciferol which are synthesised in the body from sunlight exposure or derived from dietary sources such as oily fish, butter, eggs, liver and milk. Although the sun is an excellent source of vitamin D there is no accurate way of measuring how much is being taken. But lack of sun exposure has been found to be an independent risk factor for the development of osteoporosis (Paganini-Hill *et al*, 1981). With age the ability to convert vitamin D to its active metabolite calcitriol declines. In addition, there is evidence to suggest that vitamin D deficiency may exacerbate muscle weakness and thus contribute to falls and fractures (Resnick *et al*, 1989).

Figure 9 **Cortical bone mass of Yugoslavian women living in high versus low calcium districts**



Source Redrawn from Markovic *et al* (1979).

On this basis supplemental vitamin D should be beneficial, particularly for elderly women who are often deficient in vitamin D. However, although vitamin D treatment increases intestinal absorption of calcium there is little support for its use alone in the prevention and treatment of osteoporosis since it also increases bone resorption (Resnick *et al*. 1989) and plasma and urine calcium. Thus treatment does not appear to have a net positive effect on calcium balance (Nordin *et al*. 1980). In established osteoporosis vitamin D preparations do not reduce

the rate of cortical bone loss nor the rate of deterioration of the vertebrae. Some studies have actually found that treatment of a group of 70 year old women with activated vitamin D produced a small but significant increase in vertebral fracture rate (Jensen *et al*, 1982). Clearly further research should be undertaken to explain the apparent discrepancies between the beneficial effects of vitamin D in the diet and the adverse effects of vitamin D supplements on bone formation and resorption.

Fluoride is one of the most effective stimulators of sustained bone deposition (Woolf *et al*, 1988) and has been found to be effective in reducing the risk of vertebral fracture (Mamelle *et al*, 1988). The increase in bone formation contrasts with the effect of oestrogens which inhibits bone resorption. In a study undertaken in the United Kingdom, Ansell and Lawrence (1966) compared the two towns of Watford, Hertfordshire (water supply fluoridated to 2mg per litre) and Leigh, Lancashire (water supply fluoridated to 0.1mg per litre). A significantly higher bone density was found in the women in Watford, although fluoridation of the water had only taken place five years previously. This is consistent with the fact that the teeth of children in areas with fluoride depleted water supplies which have subsequently been fluoridated have increased strength, density and resistance to dental caries. Fluoride may have an important role to play in the identification of those at risk of developing an osteoporotic fracture. In the prevention and treatment of osteoporosis, concerns about adverse side effects and long-term safety have limited the use of fluoride therapy to those patients for whom alternative therapies are contra-indicated.

Recently it has been noted that reduced oestrogen production leads to a decline in the level of circulating calcitonin (Gennari *et al*, 1987), calcitonin levels increase during pregnancy, lactation and hormone replacement therapy. Calcitonin is a hormone secreted by the parafollicular cells of the thyroid. It inhibits the absorption of bone by directly affecting the activity of the osteoclasts and reducing their lifespan. Levels of circulating calcitonin are much higher in men than in women. In a study conducted over a six month period genetically engineered human calcitonin was administered for five days in every three week period combined with oral phosphate (Rasmussen *et al*, 1980). It was found that this combination increased trabecular bone volume compared with controls. Cortical bone mass remained constant but fell in the controls. However, there is no information on the long-term effects of treatment nor regarding the prevention of fracture.

Alcohol

Alcohol has been shown to have a negative effect on bone mass. Hutchison *et al*, (1979) found that a history of alcoholism substantially increased the risk of hip fractures and Paganini-Hill *et al* (1981) discovered that risk of hip fractures in women increased with consumption of alcohol. Alcoholic men have been found to have lower bone mass than non-alcoholics (Seeman *et al*,1983) but whether or not moderate consumption of alcohol causes significant loss of bone is still uncertain.

The association between osteoporosis and alcoholism may result from

a direct toxic effect of alcohol or the result of poor nutrition, reduced body weight, cigarette smoking, reduced physical activity, liver disease, factors associated with alcohol consumption. Regular use of alcohol may also contribute towards an increased risk of fracture by predisposing towards falls.

Cigarette Smoking

There is a strong association between cigarette smoking and risk of fracture. Most studies have concluded that women who smoke have a greater risk of hip, vertebral, and Colles' fractures than women who do not smoke; postmenopausal women who smoke also appear to have a lower cortical bone mass although there does not appear to be a difference among premenopausal women (Baron *et al*, 1987). There are several possible explanations for the difference in bone mass between smokers and non-smokers. Generally female cigarette smokers are thinner than non-smokers and Lindsay *et al* (1976) reported that this difference in body weight entirely accounted for the differences in cortical bone mass. But both Williams *et al* (1982) and Daniell (1976) found that both smoking and thinness added independently to the risk of hip and Colles' fractures in women. Seeman *et al*, (1983) noted that smoking was a risk factor for vertebral fractures even after adjusting for differences in weight.

Another possible reason for the difference in bone mass between female smokers and non-smokers is that women who smoke have lower serum concentrations of endogenous oestrogens (MacMahon *et al*, 1982) and lower concentrations of oestrogens during hormone replacement therapy than women who do not smoke. Women who smoke also undergo the menopause at an earlier age than women who do not, and even 'passive smokers', women who live with heavy smokers, have been found to have earlier menopause (Lindsay *et al*, 1976), the effects of which may reduce postmenopausal bone mass (Kaufman *et al*, 1980).

Medications

Certain medicines have been found to increase the risk of osteoporosis by reducing bone mass whilst others have been found to increase bone mass.

In 1932, osteoporosis was described in Cushing's original patients with excess endogenous glucocortoid and has been recognised as a complication in the use of corticosteroids or adrenocorticotrophic hormone since they were first introduced in the late 1940s. The extent to which bone mass is affected reflects both the duration of the treatment and the dose. Fractures, however, have been reported as occurring within weeks of commencing corticosteroids.

Footnote: A number of substances to which the body is exposed act as induction agents for liver mitochondrial enzymes and cytochrome P450 which could result in the metabolism of both endogenous and exogenous substances being accelerated. Alcohol and 3:4 benzpyrene a common component of cigarettes both serve to induce enzymes. The association of osteoporosis with alcohol and cigarette smoking probably relates to the greater rate of destruction of oestrogen hormone and dietary vitamin D (Griffin *et al*, 1987).

Corticosteroid treatment decreases bone formation and increases bone resorption (Nordin *et al*, 1984). The decreased formation is most evident in trabecular bone, particularly the vertebrae and ribs. Osteoporosis induced through the use of corticosteroids affects men as well as women (although they are at less risk) and children as well as the elderly.

In contrast the risk of hip fracture has been reported to decrease significantly with increasing duration of thiazide diuretic useage. There has been no such trend with the use of other diuretics used in the treatment of hypertension (Ray *et al*, 1987). It is believed that thiazides decrease the risk of hip fracture by retarding age-related bone loss.

Falling

Decreased bone mass does not appear to be the only explanation for the rising incidence of hip fractures with age (Aitken, 1984). It is thought that the combined effect of decreased bone mass and an increased frequency of traumas results in an increased risk of osteoporotic fracture with age (Melton, 1984). For the elderly prevention of falls may be the most promising way of preventing osteoporotic fracture.

More than one in three people over the age of 65 will have a minor fall each year (Resnick *et al*, 1989) although only a small minority will experience a fracture. Like the incidence of hip fracture the risk of falling and related injuries increases with age in both sexes and the risk of falling is greater among females than among males. Sheldon (1960) found that among patients aged over 50 years of age women fell four times more often than men and the incidence of falls rose exponentially with age up to 85 years.

There are many causes of falling in the elderly and often these factors interact to cause falling so that falls are attributable to several factors. These factors can be divided into two groups: host factors such as diseases or decline in neuromuscular function with age and environmental factors.

Balance is often impaired as is mobility with increasing age, there is progressive muscular weakness and reflexes are slowed or non-existant. Vision may also be impaired and if not corrected can lead to tripping over unseen objects. In addition the elderly may be slightly confused. All these factors increase the risk of falling and if they do fall because their reflexes are slower and muscles weaker they are less able to protect themselves against the impact of the fall than a younger person. Certain illnesses may affect mobility and stability, for example Parkinson's disease and arthritis and confinement to bed with an illness such as pneumonia is often followed by a deterioration in balance and coordination (Woolf *et al*, 1988). The sudden loss of consciousness as a result of blackouts, fainting, epileptic fits and cardiac problems followed by confusion and disorientation on recovery may account for up to 25 per cent of all falls in the elderly (Woolf *et al*, 1988).

Medicines are also an important cause of falling. Many of those prescribed for the elderly to combat other diseases increase the liability to fall. For example, those given to reduce blood pressure, particularly diuretics and vasodilators are the commonest causes of postural hypotension. The risks of falling, fracture and even death are such that they

may outweigh the benefits of using hypertensives (reduction in heart failure or stroke) in the very old (Woolf *et al.* 1988). It may therefore be more appropriate in such cases to use a thiazide diuretic which, as previously mentioned, appears to decrease the risk of hip fracture by slowing age related bone loss (Ray *et al.* 1987). Sedatives such as benzodiazepines (ABPI Data Sheet *Compendium*, 1988) may have a major affect in that many falls occur in the bedroom when stumbling around in the half light.

Not to be forgotten are the effects of alcohol on the body's co-ordination and balance which may be a factor in many falls. Some elderly people may consume more than might be expected whilst others are simply more sensitive to the effects.

Although environmental factors, such as trailing wires, stairs and loose rugs, almost certainly contribute to falls and injury in the elderly there is little evidence to indicate the extent of the problem. Wild and Nayak (1981) estimated that about 25 per cent of falls for which medical attention was sought during one year in Birmingham involved an environmental factor, but there is often another risk factor present, for example, the combination of a steep step and poor eyesight. Most falls and fall related injuries in the elderly occur in the home. Loose rugs, steep stairs and slippery or uneven walking surfaces are obvious hazards and potential causes of falls. For people with reduced neuromuscular, mental or perceptual capacities any obstacle to routine daily activities is potentially hazardous. Stairs are a common cause of falls. The frequency with which they are involved is out of all proportion to the amount of time actually spent on them (Sheldon, 1960).

Incidence of fractures, particularly the hip and wrist, rise in winter (see Table 7). Given that the weather is bad and pavements are slippery with ice or snow this fact might be expected. However, as stated, the vast majority of all accidents occur within the home. In a study of elderly women admitted to hospital with fractured neck of femur Bastow *et al.* (1983) noted that there was a mid-winter peak in fracture incidence and a marked nutritional variation in the type of patient admitted. A much

Table 7 **Deaths from fractured neck of femur: month of occurrence: England and Wales 1984**

	Month					
	Jan	*Feb*	*Mar*	*Apr*	*May*	*Jun*
Male	34	28	31	39	29	24
Female	106	91	114	112	108	71
	Month					
	Jul	*Aug*	*Sept*	*Oct*	*Nov*	*Dec*
Male	32	23	18	29	24	30
Female	85	77	82	91	90	116

Source OPCS 1984.

higher proportion of thin patients presented in winter after accidents indoors. The authors found that thinness or under nutrition impaired thermoregulation and predisposed towards hypothermia, lack of co-ordination and accident.

Measurement of risk of fracture

As yet there is no entirely satisfactory method of identifying those at risk of fracture before the event. Many of the techniques currently available measure bone mass in the appendicular skeleton (limbs). It is often assumed that measurements of bone mass made in the appendicular skeleton (limbs) reflect low bone mass at sites where fractures occur and this is not entirely correct (Johnston, 1983). Measurements in the appendicular skeleton do show changes in bone mass with ageing but they do not correlate closely with age-related fractures. This is due to the fact that the areas of the skeleton generally measured, the metacarpals and the middle of the forearm are predominantly comprised of cortical bone and therefore do not adequately reflect the changes in trabecular bone status in osteoporosis related fracture sites such as the hip and vertebrae.

Dual-photon absorptiometry and quantative computerised tomography can accurately and reproducibly assess bone mass at both these sites (Fogelman, 1988a) and in addition are able to provide a reasonably accurate measurement of the total cortical and trabecular mineral content of the bone (Chestnut, 1987). The technology of both these methods is complicated. In addition, dual-photon absorptiometry is expensive (each machine costing in the region of £40,000) and also time consuming to operate, one patient assessment taking up to half an hour. Thus the use of this technique is not practical for routine mass screening programmes (Aitken, 1984). At present there are only 12 of the machines in the United Kingdom (Fogelman, 1988b). However, the equipment is improving all the time and a second generation dual photon absorptiometry machine has recently been developed. The dual energy X-ray scanner not only appears to be able to offer very precise measurements but also much quicker scanning times which could lead to a wider clinical application and have important implications for the establishment of a mass screening programme. Cheaper and simpler methods of measurement are also available like single-photon absorptiometry and hand radiographs. Unfortunately these generally measure the appendicular skeleton.

Although reduced bone mass is an important determinant of fracture risk even this may not be an accurate way of predicting the risk of fracture in the individual. All adults lose bone as they age but only a minority sustain a fracture. In studies individuals with hip fractures do appear to have lower bone mass than controls of a similar age and sex but there is some degree of overlap and the difference that does exist does not seem to be large enough to be the primary determinant of who will experience fractures (Cummings, 1985).

Most hip or Colles' fractures occur as the result of a fall, consequently the tendency to fall or the inability to protect oneself against falling is

important in determining who will experience a fracture. Muscle weakness and neurological disorders can lead to an increased risk of falling and the degree and frequency of trauma is an important determinant of fracture. It has also been suggested that the local bone geometry, the fat content of the bone and the accumulation of microscopic fractures in the bone (Mazess, 1983) might also be an important determinant of fracture.

Since it appears that measurement of bone mass whether in the hip, spine or limbs cannot reliably differentiate between individuals who will get fractures and those who will not, to prevent fractures occurring the most positive approach to avoiding fractures seems to be general prevention. This must involve either preventing osteoporosis among all postmenopausal women and the elderly or by identifying and preventing other factors that determine which osteoporotic patients will sustain fractures.

Prevention and treatment of osteoporosis and osteoporosis fracture

At present there are two possible courses of action for the prevention of osteoporotic fracture. Firstly, the strength of bone might be increased. Measures that might substantially increase bone strength are largely experimental and ways in which bone mass can be effectively increased are unknown therefore this course of action needs to be focussed mainly on interventions aimed at the prevention of bone loss. Secondly, injuries that result in fractures may be prevented. Since most of these injuries occur in the elderly as a result of falls, this course of action is best focussed on the prevention of falls.

Of all types of osteoporotic fractures, hip fractures account for the greatest mortality, morbidity and expense. Therefore hip fractures should be the primary focus of preventive measures. The best method of preventing hip fractures depends on age (Cummings *et al.* 1986). Measures to prevent bone loss are likely to be much more effective in younger people who have a greater bone mass than in the elderly who are already osteoporotic. For the elderly, interventions to protect against falls will be the most beneficial since they have the highest incidence of falls. In addition, treatment of established osteoporosis is difficult and therefore it is better to prevent the condition.

Screening

Bone Density

Screening for osteoporosis is controversial, particularly those methods which measure bone mass. There are those who believe that bone mass is the single best predictor for the risk of osteoporotic fracture whilst others argue that low bone mass has not been causally linked with increased risk of osteoporotic fracture later in life.

If it could be shown that low bone mass could be used to predict risk of fracture this would provide some justification for widespread screening for osteoporosis. Women would have at least one bone mass measure-

ment at the time of the menopause to assess whether they have high, average or low bone mass. Those with low bone mass would be treated immediately, those with high bone mass would be reassured and would remain untreated. Those with average bone mass would be asked to return for a repeat measurement in three years (Fogelman, 1988).

However, one such screening measurement of bone density may not be sufficient for two reasons: firstly, bone density if measured in the forearm does not accurately reflect the bone density of more clinically relevant sites such as the vertebrae and the hip, although statistical adjustments might be made; secondly, one measurement will only show bone mass at that point in time but will not show the rate at which bone mass is being lost (Diagram 1). Even two measurements to determine the rate of bone loss may produce estimates which are imprecise and misleading (Cummings *et al*, 1986).

In 1989 a single measurement of bone density is estimated to cost: using single photon absorptiometry £50; using dual photon absorptiometry or dual X-ray for a single site £80; and CT scan £100–150. These costs would obviously be reduced, perhaps by as much as 50 per cent if the measurements were used on a large scale or as part of a mass screening programme. Measurements of bone mass as a method of screening has an additional problem in that there is little available data on which to set a standard for bone density although hopefully this problem will be rectified by research currently being undertaken.

Bone Turnover

Danish researchers (Christiansen *et al*, 1987) have shown that it may be possible to detect those with a fast bone turnover by measuring blood levels of alkaline phosphatase and urine levels of calcium and hydroxyproline in conjunction with measurement of height and weight. Christiansen *et al* using this method were able to identify 79 per cent of fast bone losers and 78 per cent of slow bone losers. These simple tests would have obvious advantages for a GP based screening system. A further advantage of the approach over serial (at least two) bone mineral content measurements (which would identify almost 100 per cent of fast losers) is that it identifies the majority of fast losers early in the postmenopausal period before bone mineral content has fallen substantially thus ensuring, where necessary, early treatment.

Risk Factors

The well-known risk factors for osteoporosis such as previous fracture thought to be due to osteoporosis, early menopause, caucasian race, family history, smoking, high alcohol intake, and steroid therapy (see Table 8) may also be used as a method of screening. Although this method is rather haphazard and cannot differentiate between fast and slow bone losers it has been suggested that in the absence of a more accurate method, treatment should be considered for patients presenting with two or more of the indicated risk factors (*Drug and Therapeutics Bulletin*, 1989).

The value of any screening programme for osteoporosis is very much dependent upon the treatments which are available and the decision

Table 8 **Risk factors for Osteoporosis and fracture**

Principal Risk Factors	*Effects on the development of Osteoporosis*
Early Menopause	Oestrogen protects against bone loss.
Parity	Women have a greater risk of developing osteoporosis if they have not had children.
Race	Black people have higher skeletal mass and lower incidence of osteoporosis than whites and asians.
Family History	Osteoporosis is hereditary. Daughters of women with postmenopausal osteoporosis are at increased risk of developing osteoporosis.
Body Build	Obesity protects against postmenopausal bone loss by increasing the amount of available oestrogen. Greater weight means that more stress is put on the bones which leads to new bone formation.
Immobility	Prolonged bed rest and immobility leads to decreased bone mass in young and old.
Low Calcium Diet	Calcium is essential for bone formation. Many women have low intakes because they avoid high calorie dairy products.
High Protein Diet	Excess protein consumption increases calcium excretion.
Low Fluoride Diet	Fluoride stimulates bone formation.
Smoking	Women who smoke have lower body weights and earlier menopause than non-smokers.
Alcohol	Heavy alcohol consumption leads to a decline in bone mass and an increase in the risk of falling.
Steroid Therapy	Corticosteroid therapy decreases bone formation and increases bone resorption.

about whom to treat. Clearly, a national screening programme is of little value if it is decided to treat all menopausal women. However, if it is decided to treat only those women at high risk of developing osteoporosis then some method by which they can be identified is required.

The decision about whether to treat all menopausal women or only those at high risk of developing osteoporosis is likely to be based on the cost and duration of the treatment and the associated benefits and risks. There are various therapies currently used in the prevention and/or treatment of osteoporosis. These include hormone replacement therapy (HRT), either oestrogen on its own or with sequential progestogen, calcium supplements, calcitonin, fluoride and regular exercise. Anabolic steroids and vitamin D supplements are also used.

Hormone Replacement Therapy

A woman in the United Kingdom can now expect to live between 25 and 30 years after the menopause, one third of her life. A decline in the production of oestrogen at the time of the menopause may result in several clinical syndromes ranging in severity from minor to life threatening, from hot flushes to hip fractures. It is estimated that 75–85 per cent of post-menopausal women will develop symptoms related to oestrogen deprivation (Hammond *et al*, 1982). Few regimens are effective in the treatment of these problems other than hormone replacement therapy.

Yet few therapies have generated as much controversy and aroused as much media attention as has HRT. There appears to be two main reasons for the controversy which surrounds HRT. Firstly, during the 1970s a link between exogenous oestrogen and endometrial cancer was demonstrated, this led many doctors to avoid prescribing HRT. However, it has been found that when oestrogen is given in combination with progestogens the risk of developing endometrial cancer returns to the baseline and may even be reduced.

The second area of controversy is the relationship between the normal ageing process and the development of postmenopausal symptoms. Some would argue that the symptoms experienced following the menopause are a natural part of ageing and therefore should not be interfered with. But studies have shown that at least three major syndromes (hot flushes, urethrovaginal atrophy and postmenopausal osteoporosis) are specifically related to oestrogen deprivation which can occur at any time in women after natural or induced ovarian failure. The benefits of HRT for women with these conditions are dramatic.

A decline in the production of oestrogen at the time of the menopause results in increased resorption of bone. If the bone mass of women who have had their ovaries surgically removed is compared with that of women who have had a natural menopause the significant variable is not chronological age but years since ovarian failure. In a study of 220 osteoporotic women who were treated with HRT for a total of 1,869 patient years the expected fracture rate of 40 per 1,000 patient years was reduced to 3 per 1,000 (Gordon *et al*, 1973). It is clear that oestrogen deprivation plays an important role in accelerating osteoporosis and that oestrogen replacement significantly delays it. Hormone replacement therapy is much more effective in slowing the development of osteoporosis than in treating it once it has occurred.

The cost of prescribing hormone replacement therapy is approximately £46 per annum (1989 prices) with a recommended duration of treatment of up to ten years or not later than 65 years of age. After 65 years of age or ten years of therapy bone is lost at a rate comparable with that of untreated women (Lindsay, 1988). If it is taken that the menopause commences at 50 years of age at which point treatment starts, the annual prescription cost will be £46 multiplied by 2,727,400 (number of women aged between 50 and 60 in England and Wales in 1985) giving a total annual cost of £125 million.

The direct hospital costs of hip fractures in 1985 in England and Wales was £128 million, in 1988 it was estimated that the cost to the National Health Service of all osteoporotic fractures was £500 million (*Women's*

Health Concern, 1989). It is estimated that in treating postmenopausal women with HRT hip fracture occurrence might be reduced by almost 50 per cent (Melton *et al*, 1986). If in 1985 HRT had been previously prescribed for the 25 per cent of women at high risk (subject to their accurate identification) and there had been a 50 per cent reduction of incidence there would have been a saving of £64 million on the cost of hip fracture alone. With a prescription cost of £31.25 million this would have resulted in a net financial saving of £32.75 million.

In 2011 it is calculated that there will be 15,587 hip fractures among women aged 75–84 at a cost of £478 million (based on an annual inflation rate of 10 per cent). In 1985 if the 25 per cent of women, aged 50 to 54, at high risk of hip fracture had been correctly identified and treated with HRT for a period of ten years at a prescription cost of £169 million (calculated by inflating to the mid-point, 1990) and there was a 50 per cent reduction in the number of hip fractures in 2011 there would be a net financial saving of £70 million. More widespread treatment of women at the menopause with HRT may be advantageous in terms of the relief of menopausal symptoms and the possibility of protection from ischaemic heart disease although in terms of the avoidance of hip fractures alone it would not be cost-effective.

However, there are also other effects associated with the use of HRT. Up to 75 per cent of women receiving sequential oestrogen and progestogen will experience light cyclical bleeding. For some women, this is not acceptable particularly some years after the menopause. HRT may also cause breast tenderness, the return of premenstrual tension and sometimes weight gain. Dry eyes have been noted by some opticians.

Established breast cancer has been found to be oestrogen dependent and HRT should not be given in these circumstances. Several studies have investigated the relationship between HRT and the development of breast cancer, unfortunately, the results have been conflicting. Several large studies have looked for an increased risk of carcinoma of the breast following HRT and failed to find an association, but a recent study of 23,244 women over the age of 35 in Sweden (Bergkvist *et al*, 1989) found an increased risk of breast cancer in those women taking unconjugated oestrogens,* relative risk of 1.1 overall rising with duration of therapy to 1.7 after nine years. However, unconjugated oestrogens are only taken by a minority of women in the United Kingdom and this study failed to find any association between the development of breast cancer and the use of conjugated oestrogens. A higher risk was noted in women taking the combination of oestrogen and progestogen, relative risk 4.4 after six years, but this result was based on only 12 women. Clearly further research needs to be done on the association between breast cancer and the use of HRT, particularly the use of the combination of oestrogen and progestogen which is commonly prescribed in the United Kingdom.

As previously discussed there is a risk of developing endometrial cancer with the use of oestrogen unopposed by progestogen. However, it has been shown that the use of progestogens in combination with

*Conjugated Oestrogens are oestrogens combined chemically with glucuronic acid, recovered from equine urine.

oestrogens for minimum of ten days per month reduces the incidence of endometrial cancer to minimal levels and may even be protective.

Premenopausal women have a lower rate of ischaemic heart disease than men. After the menopause the prevalence increases and eventually becomes the same as men. It appears that exogenous oestrogens have a protective effect on the risk of fatal ischaemic heart disease (Ross *et al.* 1981). It is not certain whether this protection is also given with the use of combined oestrogen and progestogen.

Oestrogen replacement therapy has been found to reduce the increased risk of cardiovascular disease in postmenopausal women (Bush *et al.* 1983) as a fall in mortality (particularly myocardial infarction) has been demonstrated in the United States (Bush *et al.* 1985). A recent survey of 1,057 women in the United States between 1984 and 1987 published in the *Journal of the American Medical Association* (JAMA, 1989) found that the use of postmenopausal oestrogens either alone or in combination with progestogen was associated with a reduction in heart disease risk factors. If confirmed, this is of major importance in the use of oestrogen replacement therapy since cardiovascular disease is a major cause of death among postmenopausal women and would undoubtedly outweigh the risk of endometrial or breast cancer.

In 1985 there were 6,285 discharges and deaths from IHD among women over the age of 50 in England as compared to 634 discharges and deaths from endometrial cancer among women in the same age group. In 1985 direct hospital costs for these conditions were £7.7 million and £585,000 respectively. A randomised clinical trial is obviously needed to evaluate the differences in risk factors for heart disease in users of unopposed and opposed oestrogens to establish the relative merit of these regimes which until recently have been primarily based on the expected protection of the endometrium (Barrett-Connor *et al.* 1989). Ischaemic heart disease and cardiovascular disease are much more common causes of mortality and morbidity than endometrial cancer and therefore the effect of HRT on risk factors for heart disease must be included in prescription planning (Hillner *et al.* 1988).

Based on currently available data relating to the benefits and risks of oestrogen and progestogen in the prevention of osteoporosis and related fractures it would appear that HRT is cost-effective.

Calcium Supplements

Supplemental calcium is more expensive than HRT at around £54 for a year's supply of effervescent calcium lactate gluconate tablets. There appears to be little or no evidence of hazardous overdosage and although the formation of calcium and calcium containing stones in the urinary tract is listed as a contraindication there is little clinical evidence to support this advice (Woolf *et al.* 1988).

The most significant deficiency of osteoporotic bone is calcium and dietary calcium has been shown to be of vital importance in the attainment of a high peak bone mass at approximately the age of 30. A recently published study by the British Nutrition Foundation (1989), found that an adequate supply of dietary calcium up to the age of 30 was more important in preventing osteoporosis than calcium tablets later.

Whilst there is evidence to suggest that calcium supplements will reduce the amount of bone lost in postmenopausal women the role of calcium supplements in the prevention or treatment of osteoporosis in the elderly is uncertain (Resnick *et al*, 1989).

Calcium supplements cannot therefore be considered to be an effective alternative therapy to HRT and should only be prescribed for women with calcium deficient diets or who are unable, for clinical reasons, to take HRT.

Calcitonin

The use of calcitonin may be considered in the primary prevention of osteoporosis in women at high risk for whom HRT is contraindicated. There have been few properly controlled long-term studies of calcitonin therapy in osteoporosis and at present, although calcitonin may be effective in reducing subsequent bone loss in patients with established osteoporosis, there is no substantive evidence to suggest that it reduces the frequency of osteoporotic fractures. In a study by Overgaard *et al* (1989) it was found that salmon calcitonin given intranasally prevented bone loss in the spine of postmenopausal women but did not affect the peripheral skeleton. As yet intranasal formulations of calcitonin are still under investigation in the United Kingdom.

Although minor side effects such as nausea, vomiting and flushing are not uncommon, treatment with calcitonin is virtually without complication. The main reasons for its current limited use in the United Kingdom is its high cost, approximately £8.00 per day, and the necessity for administration by injection. Long-term studies are needed to determine whether patients with osteoporosis will become resistant to the effects of calcitonin. At present the data available only shows an effect over periods between twelve and eighteen months (Woolf *et al*, 1989), which is not really sufficient for use in senile or postmenopausal osteoporosis.

Fluoride

Floride therapy appears to be effective in increasing trabecular bone mass in patients with severe vertebral osteoporosis (Riggs *et al*, 1982). In a two year randomised prospective trial in patients with vertebral fracture, 180 people given sodium fluoride 50mg per day together with calcium and vitamin D had a fracture rate of 39 per cent; 136 people on other treatments (no fluoride) had a fracture rate of 51 per cent. Pain in the ankle or foot occurred in 15 per cent of patients taking the fluoride but treatment was continued (Mamelle *et al*, 1988).

Adverse effects of fluoride therapy are experienced frequently with up to 50 per cent of patients suffering rheumatic or gastrointestinal symptoms. Nausea, vomiting, epigastric pain, diarrhoea and also occasionally gastrointestinal bleeding have been reported. Rheumatic symptoms include synovitis of the large joints and plantar fasciitis. Despite these side effects in only about 10 per cent of patients does treatment have to be withdrawn. The incidence of side effects improves with reduction of the dose.

Fluoride therapy would seem to have a role in both the prevention of

osteoporosis, as demonstrated by the studies on bone mass and the fluoridation of water (Ansell *et al*, 1966; Simonen *et al*, 1985), and in the treatment of osteoporosis, particularly in patients presenting with vertebral fracture, since it has been found to reduce the risk of subsequent vertebral fractures. But, concern about its adverse effects and its long-term safety has limited the use of fluoride therapy, and its use is generally confined to patients in specialist centres who have already experienced a fracture. It appears to be both safe and necessary to treat patients for five years but after this time its effectiveness is diminished and after ten years there is a risk of fluorosis, leading to defective mineralisation of bone, suggesting osteomalacia.

Exercise

Immobilisation can lead to bone loss (Donaldson *et al*, 1970), which on resumption of weight bearing can be at least partially reversed (Editorial *Brit Med J*, 1987). There is sufficient evidence to suggest that women should be encouraged to keep up a reasonable level of activity. With moderate exercise of 30 minutes per day walking, jogging or dancing bone loss in postmenopausal women can be reduced. One hours walking twice a week for eight months was found to increase bone mineral content of the spine by 3.5 per cent as compared with a decrease in controls of 2.7 per cent (Krolner *et al*, 1983). However, this is only half the effect reported with oestrogens (*Drug and Therapeutics Bulletin*, 1989). In addition, exercise has not yet been shown to prevent fractures, although improved muscle tone will almost certainly reduce the likelihood of falling particularly among the elderly (Block *et al*, 1987).

Exercise is potentially a two-edged sword since it might actually if performed incorrectly increase the risk of accident and fracture (Resnick *et al*, 1989). However, apart from the time spent in exercise there are few costs involved and the benefits of gentle, careful exercise outweigh any associated risks.

Other Therapies

Other therapies used in the prevention and treatment of osteoporosis include anabolic steroids and vitamin D. Anabolic steroids have a doubtful place in the prevention of osteoporosis because of their associated side effects, fluid retention, virilisation, hyperlipidaemia and cholestasis. They have been found to increase bone mass in women with established osteoporosis, probably by increasing bone formation but have not been shown to prevent fracture. In a double-blind randomised control study of postmenopausal women by Chestnut *et al* (1983), it was found that bone formation was increased in the treated group but the findings were not significantly different from those in the controls.

In addition, in this study it was found that 76 per cent of patients experienced an adverse reaction, this did not result in cessation of therapy. Chestnut *et al* (1983) also found other adverse effects, such as increased facial hair in 30 per cent, ankle oedema in 22 per cent and acne in 9 per cent. Another potentially more serious side effect of anabolic steroids is that they are known to increase total cholesterol upsetting the balance between low and high density lipoproteins and

consequently may predispose patients towards ischaemic heart disease. These effects together with increased risk of primary liver cancer precludes the long-term use of anabolic steroids (Griffin *et al*, 1987).

Vitamin D has also been found to have no role in the management of osteoporosis except where it is deficient. Many studies have shown that pharmacological doses of vitamin D are ineffective in the treatment of osteoporosis and may even be harmful. Despite this they are still commonly prescribed.

Conclusion

From both an economic and a health standpoint the most effective treatments for osteoporosis are primary prevention and preventive therapy. Both osteoporosis and osteoporotic fractures can largely be prevented given adequate resources, both for health education and effective preventive measures.

Health education is of major importance in any initiative concerning the prevention of osteoporosis. In the long-term, health education at school provides an opportunity to reduce the number of future cases of osteoporosis. Opportunities to encourage a healthier lifestyle and diet exist not only in the classroom but also in the dining-hall and on the sportsfield.

During childhood and early adulthood bone mass is being developed and built up. The effects of diet and exercise are of primary importance during this period of growth. Whilst the role of exercise during this time is generally recognised in schools as being important it is often under valued in practice. This is particularly the case for girls, who in later life are at most risk of developing osteoporosis. Academic, social and cultural pressures often discourage girls from taking part in sporting activities and few women, after leaving school, take any form of exercise. This may in part be a result of the lack of sporting activities provided by local authorities specifically geared towards women.

It is even more difficult to ensure that schoolchildren receive a healthy calcium rich diet and school meals, where supplied, should encourage healthy eating habits. Although other factors may also have played a part, a faster growth rate and improved final stature of children were observed following the pre and post-war provision of free or cheap milk to children in the UK. The provision of milk in schools continued until the early 1970s.

General practitioners are in a unique position in the prevention of osteoporosis. However, their potential contribution to reducing the incidence of osteoporosis both in the short-term and in the long-term is not being fully realised. A large proportion of doctors appear reluctant either to advise patients on diet or suitable exercise or to prescribe therapies for the prevention and treatment of osteoporosis. A surprising degree of ignorance regarding osteoporosis appears to exist among the medical profession. In a recent survey of general practitioners, 20 per cent stated that they had never seen a case of osteoporosis among their

patients although the evidence suggests that one in four women in their 60s and one in two women in their 70s will suffer an osteoporotic fracture (*National Osteoporosis Society*, 1987).

The role of general practitioners and the primary care team is not only to provide advice on diet and exercise in the long-term prevention of osteoporosis but also to recognise those women at high risk of developing osteoporosis and osteoporotic fractures and to prescribe preventive medication if appropriate. Known risk factors for osteoporosis, as listed in Table 8, could easily be used by a general practitioner or another member of the primary health care team as the basis for a preliminary investigation. It has been recommended that when two or more of the listed risk factors are present HRT should be given (*Drug and Therapeutics Bulletin*, 1989) although in certain cases a doctor may wish to refer the patient for bone mass screening before embarking upon a course of treatment. This method of identifying women at risk is by no means ideal but in the absence of a mass screening programme if any effort is to be made to reduce the number of cases of osteoporotic fractures it is important that GPs learn to recognise the risk factors for osteoporosis and apply them in the care of their patients.

There is an enormous weight of data concerning osteoporosis and the possibilities for prevention and an increasing public awareness about the nature and causes of osteoporosis has led many women to conclude that it is a condition which they no longer have to suffer. Much media attention has been given to osteoporosis and especially the benefits and side-effects of therapies used in the prevention and treatment of osteoporosis such as HRT, calcium supplements and various unorthodox remedies. Calcium supplements are known to be no substitute for oestrogen in the prevention of bone loss, but for many women who do not receive adequate medical advice there may be little real alternative. Several other mineral remedies have been promoted as alternatives to HRT in the wake of increased public interest in osteoporosis. Boron, zinc and magnesium supplements in particular have received some media interest but to date there is little clinical evidence to support their use in the prevention of osteoporosis.

In the case of HRT the debate has not only been about the possible side-effects of endometrial cancer and breast cancer (the benefits of treatment, other than relief of menopausal symptoms and in osteoporosis, such as a reduction in the risk of ischaemic heart and cardiovascular disease have been largely ignored) but also about whether women should in fact 'interfere with nature', in so far as the menopause and osteoporosis are part of the natural life-cycle of women.

The benefits to be gained from hormone replacement therapy in terms of current knowledge are far in excess of any known risks associated with its use. But some women do feel strongly about the question of 'interfering with nature' and nobody would argue with their right to determine the treatment that they receive even if it involves incurring an avoidable risk of bone fractures. On the other hand every woman should be able to decide to take HRT after an informed consultation with their medical practitioner. In evidence collated by the charity Women's Health Concern it was found that many GPs refuse to prescribe HRT

even where it is clearly indicated and fail to explain their decision to the patient.

Approximately 25 per cent of women are at high risk of developing an osteoporotic fracture, particularly hip fractures, and ideally, in order that this group realise the value for them from HRT, some effective method by which they might be identified needs to be found.

The screening measures currently available are either insufficiently accurate and/or the results given are not easily reproducible therefore being unsuitable for mass screening programmes. Further research must be undertaken to assess the value of mass screening for osteoporosis and a method found by which fast bone losers can be accurately identified at the time of the menopause. In the meantime, the presence of two or more risk factors in postmenopausal women seems to be the best indicator of likely benefits from preventive measures.

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