30% of those with European names—despite their health and academic suitability being the same.⁷ What was rated as different was their “non-academic suitability”—whatever that is.

The case is not proved to the hilt that those selecting students and doctors for jobs discriminate on racial grounds, but the new report shows that 40% of white doctors and 52% of ethnic minority doctors believed that there was discrimination in their region.¹ There is enough evidence to act, and the report makes 12 recommendations on what might be done. Foremost among them is the recommendation that the Department of Health and Social Security should collect statistics on the ethnic origin of doctors and use them to evaluate progress towards abolition of racial discrimination.

In addition, health authorities should implement the race relations code of practice (few have so far done so, although it is two years old), and medical schools should adopt an equal opportunity policy.

RICHARD SMITH

Assistant editor,
BMJ

1 Anwar M, Ali A. *Overseas doctors: experience and expectations*. London: Commission for Racial Equality, 1987.

2 Veitch A. Medical schools face race investigation. *Guardian* 1987 January 30:4.

3 Community Relations Commission. *Doctors from overseas: a case for consultation*. London: CRC, 1976.

4 Smith DJ. *Overseas doctors in the national health service*. London: Policy Studies Institute, 1980.

5 Veitch A. Medical schools to face discrimination inquiry. *Guardian* 1986 December 8:4.

6 Collier J, Burke A. Racial and sexual discrimination in the selection of students for London medical schools. *Medical Education* 1986;20:86-90.

7 McManus IC, Richards P. Admission to medical school. *Br Med J* 1985;290:319-20.

Regular Review

Osteoporosis: cause and management

ROGER SMITH

Osteoporosis, for years a disease of little interest despite being common and crippling, is becoming fashionable. Not only do satellite travellers,¹ obsessive slimmers,² and women long distance runners³ seek to prevent bone loss but also many premenopausal and perimenopausal women now ask about their skeletal future. Will they lose bone and, if so, how fast? Are their bones likely to fracture and their frames to shrink? And if so what can be done?

Research provides some answers. In addition to the voluminous data on mineral metabolism, we now have some idea of how bone cells talk to each other,⁴ how mechanical forces affect the skeleton,⁵ and even what genetic factors determine bone mass.⁶ Furthermore, we can measure with some accuracy the density of bone in both the central and peripheral skeleton, although we find it difficult to interpret the results. The many reports on osteoporosis have recently been well reviewed.⁷

Despite such advances important and familiar problems remain unsolved, and new ones arise. How does bone loss occur? What is the relation between osteoporosis and fracture rate? What is the effect of calcium on the skeleton? And should perimenopausal women have their bone mass measured?

Physiology of bone loss

To understand how loss of bone occurs one should know something of its physiology.⁸ The main components of bone are cells, the organic matrix, and minerals. Of central importance is the osteoblast,⁹ which is a specialised fibroblast that synthesises bone collagen (and other components of the matrix), controls its mineralisation, receives and translates

mechanical forces, and modulates osteoclastic activity. The osteoclast, a cell of haemopoietic origin that resorbs bone, may depend on the osteoblast for many of its actions; it appears to have no receptors for parathyroid hormone or oestrogen, although it is reversibly subdued by calcitonin. The osteocytes, which are derived from surviving osteoblasts, contribute to the integrity of the bone.

Whatever its age, the skeleton is continuously being removed by osteoclasts and replaced by osteoblasts. This renewal is most rapid in the young. Where bone mass is constant—as in the young adult—these activities are precisely linked. On the surface of bones the cells work in sequence: activation of osteoclasts is followed by about two weeks of resorption; next there is a reversal phase and then for two to three months osteoblasts make new bone. This complex process works in groups of cells called “basic multinuclear units” in both cortical and trabecular bone.¹⁰

Bone mass reaches a maximum at about age 30 and then declines as the cells “uncouple” and osteoclasts begin to dominate. Endosteal resorption in the long bones outstrips periosteal formation, and cortical thickness decreases; major trabeculae are thinned in the vertebrae and elsewhere, and minor trabeculae perforated by osteoclasts may be irreversibly lost. Bone loss is more rapid in trabecular than in cortical bone because the surface area is greater. During a lifetime women lose about a third of cortical bone and half of trabecular bone, whereas men lose two thirds of these amounts.¹¹

Bone mass is in part determined by genetic factors. Some races and some families have smaller, lighter, and more gracile bones than others; and juvenile and adult radial bone mass (and width) is more closely related in monozygotic than dizygotic twins. Women have smaller skeletons than men,

although the maximum density of vertebral bone may be similar.¹² Mechanical forces and hormones act on this genetic background to determine eventual bone mass and often act in opposing directions.¹³

Causes of osteoporosis

The commonest causes of bone loss are old age, immobility, and the menopause. Less common causes (but important because of the lessons they provide) are hypercorticism, hypogonadism, hypopituitarism, and inherited osteoporosis (osteogenesis imperfecta). Idiopathic osteoporosis also occurs in young persons or related to growth or pregnancy.

How do these forms of osteoporosis come about? Perhaps the simplest to understand is osteoporosis of old age ("senile" or type II osteoporosis⁷) in which osteoblasts fail adequately to replace resorbed bone. Each osteoblast makes less bone matrix than normal¹⁴ and may respond poorly to mechanical factors. With immobility in the younger person it is the mechanical forces that are lacking: rapid uncoupling occurs and is not corrected until mobility returns. Mysteriously, osteoblastic failure is accompanied by an increase in osteoclastic resorption.¹⁵ The deleterious effect of bed rest on the skeleton has been known for years,¹⁶ and dual photon absorptiometry has now been used to confirm the loss of vertebral bone in patients confined to bed with prolapsed intervertebral discs.¹⁷

The cause of postmenopausal bone loss is still debated. Not all densitometric studies show accelerated bone loss at this time (and such loss is certainly less than after premenopausal oophorectomy). The suggestion that lack of oestrogen allows increased parathyroid mediated bone resorption has little support. Similarly, measuring plasma calcitonin concentrations in patients with osteoporosis has given contradictory results.

Osteoporosis in hypercorticism is most dramatic in Cushing's syndrome, but more common in patients taking corticosteroids; and results from reduced osteoblastic activity. In thyrotoxic bone disease rapid turnover leads to resorption being greater than formation. Hypogonadism in young men is a well known (though often unrecognised) cause of osteoporosis. Severe osteoporosis can occur in women during pregnancy: the cause seems not to be excessive bone resorption but rather failure of the usual changes in calciotropic hormones that protect the maternal skeleton.¹⁸ The cause of temporary osteoporosis associated with growth (juvenile osteoporosis) remains an enigma,¹⁹ but the aetiology of osteoporosis in osteogenesis imperfecta has recently been clarified. In its mild form the collagen output of each osteoblast is cut by about half, whereas in its most severe form helix formation is defective in three quarters of the collagen molecules because of mutant chains being incorporated. This leads to a functionally useless skeleton and perinatal death.²⁰

Recent work re-emphasises that hypogonadism is bad for the skeleton. Bone density is reduced (and corrected by treatment) in men with prolactin secreting tumours and low testosterone concentrations.²¹ In women athletes with premenopausal hypothalamic amenorrhoea and low mean oestradiol concentrations spinal (but not forearm) bone density is abnormally low.^{3,22} A reduction in radial bone density has also been recorded in women with anorexia nervosa, and vertebral fractures may occur.² In such indi-

viduals osteoporosis is probably related to the low mean oestrogen concentrations (although reversible hypercorticism occurs in anorexia nervosa) and may be overcome by vigorous exercise. Similar oestrogen deficiency presumably contributes to the stress fractures of young ballet dancers; their frequency is related to delay in the menarche and the incidence and duration of secondary amenorrhoea.²³

These rare causes of osteoporosis emphasise the interaction of mechanical, genetic, and hormonal factors on the skeleton. They also pinpoint the likely risk factors for osteoporosis: a strong family history of osteoporosis; short stature and small bones; early menopause; white or Asian race; inactivity; cigarette smoking; low calcium intake; leanness; nulliparity; and excessive alcohol consumption. Doubtless these are interrelated.

Recent work points to the bad effect of alcohol on the skeleton. Of 96 heavy drinkers attending a Veterans Administration hospital, 45 had radiographic evidence of extensive bone loss and about one third were aged 31-45.²⁵ In another study of 22 alcohol abusers six had histological evidence of osteoporosis with reduction in mean wall thickness of trabecular bone packets, supporting other evidence that alcohol directly damages bone cells.^{26,27}

Osteoporosis and fracture

Fractures in patients with osteoporosis can be seen either as mainly a problem of the bones⁷ or as mainly a result of increased falls.²⁸ Bone mass declines with age and in an increasing proportion of people reaches the "fracture threshold"—a level above which fracture does not usually occur without severe trauma. Below this "threshold" fractures are likely, but predicting who will sustain them (particularly in the hip) is virtually impossible (figure).⁷

Change in mean bone mineral density with age in the spine and femoral neck (95% confidence limits shaded grey). Fractures, represented as ● and ▲, do not occur above a certain bone density ("fracture threshold"). Below this value fractures are likely but the bone density is often within the normal range for age, especially for the hip.⁷

Despite this the commonest reason given for doing research into osteoporosis is the catastrophically high rate of fracture of the femoral neck. But reducing the rate will be possible only if the bone mass of whole populations is kept well above the fracture threshold, which is probably an unrealistic aim. What may be more important is the increased tendency of the elderly to fall because of loss of the normal protective reflexes,²⁹ hypothermia,³⁰ or over-enthusiastic drug treatment.

In a skeletal Utopia the maintenance of early adult bone mass throughout life would eliminate non-traumatic fracture (or so it is thought). In real life the doctor does not begin to deal with osteoporosis until after a fracture has occurred.

Treatment of osteoporosis with fracture

Many accounts of osteoporosis fail to mention the individual patient. If we exclude those whose first symptoms come from a broken forearm or hip the main presenting complaints are loss of height and pain in the back. Loss of stature may either be dramatic or not have been noticed; the pain is likely to come after unusual spinal stress, such as moving furniture or heavy shopping. The patient is worried whether the rapid loss of height will continue (How far will I shrink?) or whether the back pain will persist. Provided the diagnosis is correct she may be reassured on both points^{31 32}: loss of height is not linear (its apparently rapid rate is often deceptive since it may have been occurring for several years); and back pain is only intermittent (patients usually present shortly after an episode of vertebral collapse—so a period free of symptoms is likely to follow).

After giving an explanation to the patient the doctor should relieve pain (with analgesics, a temporary light support for the back, or both), remove factors likely to worsen bone loss (for example, smoking or excessive alcohol consumption), avoid stresses likely to induce fractures, and plan treatment for the future. In theory further bone loss should be minimised by stimulating formation or reducing resorption, but as these processes remain coupled, although imbalanced, no single treatment is likely to have an exclusive effect on either.

Bone formation regimens

Bone formation regimens include physical exercise or the use of sodium fluoride. Synthetic 1-34 parathyroid hormone fragments, oral phosphate (with calcitonin), and anabolic steroids have little effect. The patient with painful crush fractures of the vertebrae will find exercise difficult, but others should exercise within the limit of pain. Swimming, where the weight of the body is supported, is often acceptable.

Sodium fluoride stimulates osteoblasts and is incorporated into the bone as fluorapatite.³³ It reduces the vertebral fracture rate, especially if used with other agents such as calcium and oestrogens.³⁴ It has, however, variable and troublesome side effects, and up to a third of patients show no anabolic response. Furthermore, it may cause a redistribution of mineral within the skeleton, and the optimum dose and length of treatment are not established. For these reasons it should be used only in research centres.³³

Antiresorptive measures

Three drugs appear to act by reducing bone resorption—calcium, oestrogen, and calcitonin. There is no advantage in giving vitamin D or its metabolites unless the patient has osteomalacia. Injectable calcitonin is not used in Britain mainly because of its side effects and expense, but alternative

preparations, such as nasal sprays, may become available. Oral calcium is widely used, although there is doubt about its efficacy (see below). Oestrogen does work, but the difficulty is to decide who should get it.

Prevention

It is not (yet) possible to alter the genetic contribution to bone mass, but it must be important to establish a maximal bone mass in early adult life (regardless of the rate of subsequent decline). The main way of doing this is to use the skeleton,^{35 36} but the factors that lead to bone loss should also be avoided. If calcium has any anabolic effect on the skeleton then it is likely to be during its growing period, and the daily intake should be up to 1500 mg.

Women are likely to have three questions as they approach the menopause: Should I have my bone mass measured? Should I take additional calcium? Should I take oestrogens?

In the United States instruments for measuring bone mass are widely available, and patient demand, widespread advertisement, and likely financial reward all suggest that most women between the ages of 45-70 years should be screened for osteoporosis. Ott, however, has pointed out the fallacies of this approach.³⁷ Although bone mass measurements are accurate in the laboratories which have developed them, they are not elsewhere. Normal values differ between centres and with age, sex, and race, and the degree of bone loss varies from one skeletal site to another—so that forearm bone density will not reflect that in the vertebrae.

But even if the accuracy of "routine" measurements of bone density can be improved, using them to predict the likelihood of fractures in an individual is difficult, if not impossible (figure).³⁸ This is especially true for fracture of the hip. Additionally, the rate of bone loss is very variable.

The question of whether to take additional calcium has found recent space in *Science*.³⁹ There is a considerable evidence, including from classic calcium balance studies,⁴⁰ that calcium is good for the young skeleton and that low calcium intakes, with persistently negative calcium balances, contribute to bone loss—and Western diets contain less calcium and more fibre than they used to. The effectiveness of calcium in reducing bone loss is, however, slight or non-existent⁴¹ and has often been assessed in conjunction with other treatments—fluoride,³⁴ oestrogen,⁴² or exercise.

The National Institute of Health's recommendation⁴³ that the daily calcium intake of premenopausal women should be 1000 mg and that of postmenopausal women at least 1500 mg has not been supported by two studies that show no relation between calcium intake and bone density (including that of the spine).^{44 45} Calcium supplements will continue to be prescribed, however, on the grounds that a low calcium diet must be bad, that additional calcium does no harm (and might do some good), and that it costs little (but more than oestrogens). This state of affairs is unsatisfactory and needs urgent clarification.

The third question about the effectiveness of oestrogen seems less controversial. The evidence that oestrogens prevent bone loss and reduce fracture rate in postmenopausal women is substantial,⁴⁶ and the experience of using this treatment in younger women who have had their ovaries removed can, it seems, be carried into later years.⁴⁷ There are two main problems with oestrogen treatment: is it worth the risk, and who should be treated?

Identifying those likely to have osteoporosis (and who are therefore candidates for oestrogen treatment) has been

considered,²⁴ and the risks of taking oestrogen are being reassessed. The increased incidence of endometrial cancer (to about 1% per year) is well known but can be disregarded in patients who have had a hysterectomy. Other quoted side effects of prolonged oestrogen treatment include an increase in breast cancer, venous thrombosis, pulmonary embolism, hypertension, heart attacks, strokes, and gall stones. But the risks of these occurring (except for gall stones) have probably been overestimated, and postmenopausal women taking oestrogens may have a lower overall mortality than those not receiving treatment.⁴⁸ If this proves to be true the doctor's approach to treatment will be altered. While advantages and disadvantages of oestrogen continue to be unclear, the decision to take them still depends largely on the patient after adequate explanation by the doctor. It appears safer (and possibly more effective⁴⁹) to prescribe continuous oestrogens with intermittent progestogen (10 days out of 28), but because this may cause a return of uterine bleeding the patient may not find it acceptable.

Conclusion

The enormous amount of research in osteoporosis has led us into some difficulties. We are uncertain about the contribution of osteoporosis to the high rates of fractures in the elderly, and we cannot explain the disproportionate increase in the rate of femoral neck fracture.⁵⁰ Methods for measuring bone density do not forecast the chance of an individual fracturing a bone,⁵¹ but they do cast doubt on the usefulness of treatment with oral calcium. Qualitative as well as quantitative changes in osteoporotic bone may predispose to fracture.⁵² Improved treatments will require a better understanding of bone and particularly of the response of cells to mechanical and hormonal stimuli.

ROGER SMITH

Consultant Physician,
Nuffield Orthopaedic Centre,
Oxford OX3 7DL

- Mazess RB, Whedon GD. Immobilisation and bone. *Calcif Tissue Int* 1983;35:265-7.
- Rigotti NA, Nussbaum SR, Herzog DB, Neer RM. Osteoporosis in women with anorexia nervosa. *N Engl J Med* 1984;311:1601-6.
- Drinkwater B, Nilson K, Chesnut CH, Bremner WJ, Shainholtz S, Southworth MB. Bone mineral content of amenorrheic and eumenorrheic athletes. *N Engl J Med* 1984;311:277-81.
- Baron R, Vignery A, Horowitz M. Lymphocytes, macrophages, and the regulation of bone remodelling. *Bone and Mineral Research* 1984;2:175-243.
- Binderman I, Shimshoni Z, Somjen D. Biochemical pathways involved in the translation of physical stimulus into biological message. *Calcif Tissue Int* 1984;36(suppl):82-5.
- Prockop DJ, Kivirikko KI. Heritable diseases of collagen. *N Engl J Med* 1984;311:376-86.
- Riggs BL, Melton LJ. Involutional osteoporosis. *N Engl J Med* 1986;314:1676-86.
- Smith R. Recent advances in the metabolism and physiology of bone. In: Baker PP, ed. *Recent advances in physiology*. Edinburgh: Churchill Livingstone, 1984:317-48.
- Rodan GA, Rodan SB. Expression of the osteoblastic phenotype. *Bone and Mineral Research* 1984;2:244-84.
- Reeve J, Zanelli JM. Parathyroid hormone and bone. *Clin Sci* 1986;71:231-8.
- Mazess RB. On aging bone loss. *Clin Orthop* 1982;165:239-52.
- Riggs BL, Wahner HW, Dunn WL, Mazess RB, Offord KP, Melton LJ. Differential changes in bone mineral density of the appendicular and axial skeleton with aging: relationship to spinal osteoporosis. *J Clin Invest* 1981;67:328-35.
- Lanyon LE, Rubin CT. Regulation of bone mass in response to physical activity. In: Dixon AS, Russell RGG, Stamp TCB, eds. *Osteoporosis, a multidisciplinary problem*. London: Royal Society of Medicine, 1983:51-61. (International Congress Series 55.)
- Darby AJ, Meunier PJ. Mean wall thickness and formation periods of trabecular bone packets in idiopathic osteoporosis. *Calcif Tissue Int* 1981;33:199-204.
- Smith R. Osteoporosis—a problem of bone formation? *Postgrad Med J* 1984;60:383-5.
- Asher R. The dangers of going to bed. *Br Med J* 1947;iii:967-8.
- Krolner B, Toft B. Vertebral bone loss: an unheeded side effect of therapeutic bed rest. *Clin Sci* 1983;64:537-40.
- Smith R, Winearls CG, Stevenson JC, Woods CG, Wordsworth BP. Osteoporosis of pregnancy. *Lancet* 1985;iii:1178-80.
- Smith R. Idiopathic osteoporosis in the young. *J Bone Joint Surg [Br]* 1980;62:417-27.
- Sykes B, Smith R. Collagen and collagen gene disorders. *Quart J Med* 1985;56:533-47.
- Greenspan SL, Neer RM, Ridgway C, Klibanski A. Osteoporosis in men with hyperprolactinemic hypogonadism. *Ann Intern Med* 1986;104:777-82.
- Cann CE, Martin MC, Genant HK, Jaffe RB. Decreased spinal mineral content in amenorrheic women. *JAMA* 1984;251:626-9.
- Warren MP, Brooks-Gunn J, Hamilton LH, Warren F, Hamilton WG. Scoliosis and fractures in young ballet dancers. *N Engl J Med* 1986;314:1348-53.
- Aloia JF, Cohn SH, Vaswani A, Yeh JK, Yuen K, Ellis K. Risk factors for postmenopausal osteoporosis. *Am J Med* 1985;78:95-100.
- Spencer H, Rubio N, Rubio E, Indreika M, Seitman A. Chronic alcoholism. Frequently overlooked cause of osteoporosis in men. *Am J Med* 1986;80:393-7.
- Lalor BC, France MW, Powell D, Adams PH, Counihan TB. Bone and mineral metabolism and chronic alcohol abuse. *Q J Med* 1986;59:497-511.
- Bikle DD, Genant HK, Cann CE, Recker RR, Halloran BP, Strewler GJ. Bone disease in alcohol abuse. *Ann Intern Med* 1985;103:42-8.
- Aitken JM. Relevance of osteoporosis in women with fracture of the femoral neck. *Br Med J* 1984;288:597-601.
- Miller SWM, Evans JG. Fractures of the distal forearm in Newcastle: an epidemiological survey. *Age Ageing* 1985;14:155-8.
- Bastow MD, Rawlings J, Allison SP. Undernutrition, hypothermia and injury in elderly women with fractured femur: an injury response to altered metabolism? *Lancet* 1983;ii:143-5.
- Dent CE, Watson L. Osteoporosis. *Postgrad Med J* 1966;42(suppl):581-608S.
- Kanis J. Treatment of osteoporotic fracture. *Lancet* 1984;ii:27-33.
- Kanis JA, Meunier PJ. Should we use fluoride to treat osteoporosis? A review. *Q J Med* 1984;53:145-64.
- Riggs BL, Seeman E, Hodgson SF, Taves DR, O'Fallon WM. Effect of the fluoride/calcium regimen on vertebral fracture occurrence in postmenopausal osteoporosis. *N Engl J Med* 1982;306:446-50.
- Smith R. Exercise and osteoporosis. *Br Med J* 1985;290:1163-4.
- Krolner B, Toft B, Neilsen SP, Tonevold E. Physical exercise as prophylaxis against involutional bone loss. *Clin Sci* 1983;64:541-6.
- Ott S. Should women get screening bone mass measurements? *Ann Intern Med* 1986;104:874-7.
- Cummings SR, Black D. Should perimenopausal women be screened for osteoporosis? *Ann Intern Med* 1986;104:817-23.
- Kolata G. How important is dietary calcium in preventing osteoporosis? *Science* 1986;233:519-20.
- Heaney RP, Gallagher JC, Johnston CC, Neer R, Parfitt AM, Whedon GD. Calcium nutrition and bone health in the elderly. *Am J Clin Nutr* 1982;36:986-1013.
- Nilas L, Christiansen C, Rodbro P. Calcium supplementation and postmenopausal bone loss. *Br Med J* 1984;289:1103-6.
- Christiansen C, Christensen MS, McNair P, Hagen C, Stocklund EK, Transbol I. Prevention of early postmenopausal bone loss: controlled 2-year study in normal females. *Europ J Clin Invest* 1980;10:273-9.
- National Institutes of Health. Osteoporosis: consensus conference. *JAMA* 1984;252:799-802.
- Riggs BL, Wahner HW, Melton LJ, O'Fallon WM, Judd HL, Richelson LS. In women dietary calcium intake and rates of bone loss from mid radius and lumbar spine are not related. [Abstract.] *Journal of Bone and Mineral Research* 1986;1(suppl 1):167a.
- Christiansen C, Riis BJ, Thomsen K. Does calcium treatment prevent postmenopausal bone loss? A double-blind controlled, clinical trial. [Abstract.] *Journal of Bone and Mineral Research* 1986;1(suppl 1):166a.
- Stevenson JC, Whitehead MI. Postmenopausal osteoporosis. *Br Med J* 1982;285:585-8.
- Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomized women. *Lancet* 1980;ii:1151-3.
- Hillner BE, Hollenberg JP, Pauker SG. Postmenopausal oestrogens in prevention of osteoporosis: benefit virtually without risk if cardiovascular effects are considered. *Am J Med* 1986;80:1115-27.
- Christiansen C, Riis BJ, Nilas L, Rodbro P, Deftos L. Uncoupling of bone formation and resorption by combined oestrogen and progestagen therapy in postmenopausal osteoporosis. *Lancet* 1985;ii:800-1.
- Boyce WJ, Vessey PM. Rising incidence of fracture of the proximal femur. *Lancet* 1985;ii:1502-3.
- Cummings SR. Are patients with hip fractures more osteoporotic? *Am J Med* 1985;78:487-93.
- Kent GN, Dodds RA, Klenerman L, Watts RWE, Bitensky L, Chayen J. Changes in crystal size and orientation of acidic glycosaminoglycans at the fracture site in fractured necks of femur. *J Bone Joint Surg [Br]* 1983;65B:189-94.