LEADING ARTICLE

Osteoporosis—a problem of bone formation?

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Introduction

Osteoporosis is common, occurs predominantly in the elderly, and is virtually untreatable. For these reasons it is not a popular disorder to study; but a condition which is widely considered to be the main cause of fracture of the proximal femur, itself estimated to cost about £48 million per year in England and Wales, and to increase the death rate for age by a factor of 20 (Stevenson and Whitehead, 1982), demands our attention.

In the past those who studied osteoporosis sometimes turned the field of investigation into one of battle, and also concentrated on the changes in bone mineral to the neglect of its cells and matrix. Recent advances in bone physiology (Smith, 1984) have brought the osteoblast—and the bone matrix which it produces—back into the limelight, and now emphasize the importance of bone formation in the maintenance of bone mass. Meanwhile clinical studies have shown that the rate of femoral neck fracture has inexplicably increased out of proportion to the age of the population (Lewis, 1981), and have suggested that factors other than osteoporosis contribute to this (Evans, Ashwell and Dunstan, 1981; Bastow, Rawlings and Allison, 1983).

This selective review suggests that both the cause and the treatment of osteoporosis is best understood in terms of the osteoblast; it also cautions against the common assumption that prevention of osteoporosis would considerably reduce fracture rate in the elderly. Study of the less common forms of osteoporosis occurring at earlier ages (which include those associated with immobilization, pregnancy, hypogonadism and heparin administration, discussed in these columns) may contribute to our understanding of this disorder.

Bone physiology

Bone is a metabolically active tissue which differs

most sharply from other tissues in its mineralization. Its constantly changing structure and function are the result of cellular activity, itself controlled by many factors, particularly mechanical and hormonal. The mass of bone, which has a genetic component, depends on the balance between osteoblastic bone formation and osteoclastic bone resorption, activities which are normally closely linked or 'coupled' and have their histological expression in the basic (or bone) multicellular units (BMUs). How this 'coupling' occurs remains obscure, although local hormonal factors have been described (Drivdahl, Howard and Baylink, 1982).

Osteoporosis can be regarded as a manifestation of uncoupling in favour of bone resorption, a change in balance which could be brought about by reduced osteoblastic activity or increased osteoclastic activity, or both. The osteoblast is a specialized anabolic cell which appears to perform a variety of functions simultaneously; in particular it synthesizes all the components of bone matrix and is closely concerned with their mineralization. Evidence from independent sources has now re-emphasized its importance. Thus a series of recent studies on live osteoclasts (Chambers and Dunn, 1982) suggests that their activity may be influenced by osteoblasts, and experiments on a variety of animal models (Lanyon and Rubin, 1983) have defined how physical activity stimulates osteogenesis and maintains bone mass. These authors have shown that structurally appropriate bone remodelling can be induced by small changes in the level and distribution of strain well within the physiological range, and that the first effect of a potentially osteogenic stimulus is to prevent resorptive remodelling which would otherwise lead to disuse osteoporosis.

Further, histological measurements of mean wall thickness in human bone have demonstrated a decline in bone formation rate in elderly people (Darby and Meunier, 1981). Thus with increasing age

and in patients with osteoporosis it appears that less bone is formed at BMU level; this change alone, regardless of changes in resorption, could account for reduction in trabecular bone volume. These authors conclude that the osteoblastic components of individual BMUs are not only forming less bone but are active for a reduced period of time. Although the osteoblast responds to physical forces, and this response may lessen with age, the basic mechanisms are unknown. It is of interest to consider how far the forms of osteoporosis described in the current issue of the *Postgraduate Medical Journal* (Need, *et al.*, 1984; Major, 1984; Griffiths and Liu, 1984); can be explained as a disturbance of bone formation.

Immobilization

Failure of osteoblastic activity (alone or with an increase in bone resorption) can readily account for inherited osteoporosis (osteogenesis imperfecta), for the osteoporosis of immobilization (where external stress is removed), and for osteoporosis in the elderly.

Immobilization is a potent cause of 'uncoupling'. Not only does the rate of new bone formation decrease, but there also appears to be an increase in osteoclastic bone resorption (which is not secondary to an increase in parathyroid activity) (Mazess and Whedon, 1983). To those who look only at mineral homeostasis the reason for these changes is obscure (Stewart *et al.*, 1982); but from the cellular viewpoint both are in agreement with the Lanyon and Rubin (1983) experiments. How much of the osteoporosis in the injured man described by Need *et al.* (1984) can be attributed to his prolonged immobility is unknown since there were two other complicating factors. The first is hypogonadism, a potentially reversible cause of osteoporosis in young men (though whether hypogonadism detected only by biochemistry is relevant may be questioned); and the second is prolonged parenteral nutrition which produces its own bone problems possibly related to aluminium toxicity (Ott *et al.*, 1983).

Pregnancy

Why osteoporosis occasionally occurs in association with pregnancy is unknown, and the controversy whether this association is causal or coincidental continues. Loss of height, pain in the back and vertebral collapse occur before or shortly after delivery, and most often in the first pregnancy (Smith *et al.*, 1983). Symptoms improve spontaneously about 3 months after delivery, and subsequent pregnancies may be uneventful. Existing data do not indicate that excess bone resorption occurs; indeed, as in juvenile osteoporosis (Smith, 1980), they are more suggestive of temporary osteoblastic failure. In the patient reported by Griffiths and Liu (1984) in this journal,

heparin rather than pregnancy is considered to be the culprit, but the evidence that heparin administration leads to osteoporosis in otherwise normal people without any other cause for osteoporosis is not strong, and is certainly unlikely in the dose used in this patient. The maternal skeleton appears to be protected from the demands of the fetus by changes in calcitropic hormones, and it is possible (although not demonstrated) that relative calcitonin [or $1,25(\text{OH})_2$ vitamin D] deficiency may predispose to pregnancy osteoporosis. It is interesting that the patient described by Aarskog, Aksnes and Lehmann (1980) with low $1,25(\text{OH})_2$ vitamin D concentrations attributed to heparin was also pregnant.

Regional migratory osteoporosis

Pain around the larger joints, particularly of the lower extremity, associated with oedema, discolouration and muscle wasting, and severe periarticular osteoporosis is most likely to be called Sudeck's atrophy or algodystrophy. When the symptoms around one joint improve, often after several months, only to appear in another, the term regional or transitory migratory osteoporosis is more appropriate (Major, 1984). Although the clinical features may be localized, the association with similar osteoporotic changes in the hips, sometimes in pregnancy and with compression fractures of the vertebrae (Sutton and Robert, 1983) suggests a more generalized disorder. This disorder is frequent enough to be recognized by most physicians but its cause is unknown, and the available data too few to suggest whether or not osteoblastic bone formation is reduced.

Management of osteoporosis

To return to the bone cells; the personal view expressed here of the importance of the osteoblast logically suggests that for both prevention and treatment of osteoporosis continued physical activity is of first importance. Furthermore, it suggests that in the elderly, whose osteoblasts may be regarded as 'sleepy', physical activity should be more, not less, than in earlier years. Not all recent work supports the idea that osteoblastic activity lessens with age. Indeed Delmas *et al.* (1983) have shown that the serum concentration of the bone Gla-protein, thought to be an indicator of bone formation, increases with age in women, and is significantly high in a subgroup with fractures of the vertebrae, hip or both. It is also not wise to transfer uncritically conclusions derived from fracture of cortical bone at one site (femur) to predominantly trabecular bone at another (vertebrae) especially when the incidence of those fractures alters so differently with age (Riggs and Melton, 1983).

However there are few who would now deny the relationship between physical activity and bone mass; but agreement on the effect of other drugs used in osteoporosis is as far away as ever (Milhaud *et al.*, 1983). Oral calcium is cheap, safe and undistinguished, but recent work (Riggs *et al.*, 1982) suggests that it is better than nothing. For those interested in osteoblasts fluoride is a potential winner, since it encourages these cells to make more matrix. Unfortunately woven rather than lamellar matrix is formed and mineralization (on fluoride alone) is defective. Perhaps the most striking effects on bone (and side effects on the patient) are produced by oestrogens, and there are now convincing data that these hormones (alone, or with fluoride, or with calcium) may significantly reduce postmenopausal bone loss, by mechanisms which remain obscure (Christiansen *et al.*, 1980; Riggs *et al.*, 1982). For the present any other proposed treatments, such as calcitonin, diphosphonates and probably androgens can be dismissed on the grounds of either ineffectiveness, expensiveness or side effects.

Osteoporosis is a common disabling and potentially preventable disease. Despite a lot of work, progress has been slow with no major breakthroughs. Physicians (like other people) forget some facts as rapidly as they discover others. The ability to accurately measure bone mass, especially in the spine, is well illustrated by Krølner and Toft (1983); the fact that bed rest produces vertebral bone loss may be 'unheeded' (as the authors suggest) but is certainly not unknown (Asher, 1947). What modern techniques can now do is to demonstrate scientifically (Krølner *et al.*, 1983) that exercise can prevent this bone loss from the vertebrae (and presumably elsewhere) even in the elderly. Perhaps it is now time to take a closer look at what makes the osteoblast tick.

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