aspergillosis, since full clinical and laboratory data are available on so few patients. Ketoconazole may prove useful as a prophylactic drug in severely immunosuppressed patients. In one recent study⁸ it was more effective than topical amphotericin B and nystatin in eliminating oral fungal carriage or infection in patients with leukaemia or marrow aplasia, with the exception of those receiving allogeneic bone marrow grafts.

In clinical reports so far side effects such as nausea, headache, pruritus, and photophobia have been uncommon. Some recent reports have described probable hepatotoxicity.⁹ Liver function values become transiently abnormal in some patients and symptomatic hepatitis (cholestatic or hepatocellular) may occur in a very few patients. The incidence is probably less than one in 10 000,¹⁰ making it extremely difficult to establish a causal association; but clinicians using ketoconazole need to be aware of the possibility of liver damage with long-term treatment.

Clearly, therefore, ketoconazole is going to be a useful drug for a wide variety of fungal infections, particularly dermatophytosis, superficial candidiasis, and paracoccidioidomycosis. The response of most fungal infections to treatment varies considerably with the site of infection and the underlying condition of the patient. At present both the influence of these variables on the results of treatment with ketoconazole and the merits of the drug compared with effective alternatives are incompletely understood. The more detailed studies of keto-

conazole currently in progress will help to establish its place in antifungal chemotherapy with greater precision.

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Regular Review

Postmenopausal osteoporosis

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Osteoporosis is a diminution of skeletal mass in which bone is normally mineralised but the amount of bone tissue in a given volume of bone is reduced compared with normal. Osteoporosis may result from reduced new bone formation, increased bone resorption, or both. The most important consequence is an increase of certain fractures, which may occur either spontaneously or after minimal trauma when loss of bone has been sufficient to cause mechanical weakness. These fractures represent an end stage of the disease, and some equate osteoporosis only with the clinical syndrome of fracture due to bone loss. We consider this definition unhelpful and confusing because the diagnosis then depends on one incident which results in fracture, while the events of the previous 10 to 20 years—during which 30% of the skeletal mass may have been lost—are overlooked. In practice, therefore, we believe that the term osteoporosis should be applied when bone mass is below that expected for age and sex irrespective of whether fracture has occurred.

There are many causes of osteoporosis, the more important of which (table) must be excluded by investigation of every patient with the disorder. In adults the most common types are age-related (senile) osteoporosis and postmenopausal

osteoporosis. Aging is associated with progressive thinning of the skeleton in both sexes; this usually starts during the fifth decade in women and slightly later in men. It was established many years ago, however, that bone loss is more considerable, and consequently osteoporotic fractures more common, in women. For example, the fracture rate of the distal radius rises dramatically in women between the fifth and seventh decades but remains constant in men during this time.^{1 2}

Causes of osteoporosis in adults

Postmenopausal
Age related (senile)
Hyperparathyroidism
Hyperthyroidism
Hypercortisolism
Hypogonadism (distinct from menopause)
Myelomatosis

Metastatic carcinoma
Reticuloendothelial disorders
Connective-tissue disorders,
for example osteogenesis imperfecta
Drugs, for example corticosteroids,
heparin
Immobilisation

The concept of a second form of osteoporosis, causally related to loss of ovarian function, was first proposed by Fuller Albright *et al* to explain the increased incidence of osteoporosis and related fractures in women.³ The existence and importance of postmenopausal osteoporosis have remained controversial.

Some workers regard oestrogen deficiency as merely coincidental to age-related loss of bone.⁴ There is firm evidence, however, that this is not so and that postmenopausal osteoporosis is a distinct entity superimposed on the normal bone loss of aging. The decline in bone mass with age, at least in men, appears largely due to decreased bone formation,⁵ whereas bone loss after the menopause apparently results from an increase in bone resorption.⁶⁻⁹ Loss of ovarian function at any age is followed by a loss of bone,¹⁰⁻¹² which is particularly severe after an early menopause.¹³ This loss of bone may be prevented by exogenous oestrogens for as long as treatment is prescribed,^{14 15} yet recurs after treatment is withdrawn.¹⁵⁻¹⁷ Undoubtedly the incidence rates of the classic osteoporotic fractures are greatly reduced by long-term postmenopausal treatment with oestrogen.^{14 18-20} In general, greater benefits have been seen when oestrogens are started soon after the menopause, when prescribed for more than five years, and when given to patients who have been castrated. Hence we conclude that loss of ovarian function is the most important factor in the development of postmenopausal osteoporosis.

Though all women apparently lose bone after loss of ovarian function, not all develop the degree of osteoporosis which results in fractures. The predisposing factors are probably a low initial skeletal mass, an accelerated rate of postmenopausal bone loss, or both. Both genetic and racial characteristics affect bone mass. The mechanisms of increased bone resorption after the menopause remain to be elucidated precisely, but recent studies have shed some light and should lead to a reappraisal of previous concepts. A popular belief has been that the increased bone resorption is secondary to malabsorption of calcium,²¹ with bone calcium being mobilised homeostatically to maintain adequate plasma concentrations. Theoretically, two mechanisms might be responsible: a primary intestinal defect of calcium absorption or a primary defect of production of 1,25-hydroxy vitamin D by the kidney. If intestinal calcium malabsorption were responsible plasma calcium concentrations would tend to be on the lower side of normal with compensatory increases in the concentrations of parathyroid hormone and 1,25-dihydroxy vitamin D, the principal bone-resorbing hormones. In practice, the concentrations of parathyroid hormone and 1,25-dihydroxy vitamin D are not raised in postmenopausal women, whether osteoporotic²² or non-osteoporotic²³; indeed, these tend to be lowered. A renal defect has also been excluded, since renal production of 1,25-dihydroxy vitamin D is normal in postmenopausal women with osteoporosis.²⁴

Thus if the postmenopausal increase in bone resorption is not primarily attributable to increases in the bone-resorbing hormones or to calcium malabsorption, the concept of increased skeletal sensitivity to the actions of the bone-resorbing hormones^{25 26} becomes more tenable. Oestrogen seems unlikely to have a direct action in preventing bone resorption, since receptors for this steroid have not been found in bone.^{27 28} Probably, therefore, oestrogen controls bone resorption indirectly. Recent studies have shown that oestrogen increases the secretion of calcitonin, a hormone which does act directly on bone to reduce resorption.²³ Calcitonin may thus be the link between the administration of oestrogen and the prevention of bone resorption in postmenopausal women. Furthermore, the sex difference in calcitonin concentrations, with lower values in women,^{29 30} and the age-related decline in its secretion³¹ may render the postmenopausal woman particularly calcitonin deficient. Our current concept of the pathogenesis of postmenopausal bone resorption is that loss of ovarian function accelerates the decline in the secretion of calcitonin

which occurs with age, and as a result the actions of the bone-resorbing hormones are unopposed. Whether lack of oestrogen also leads to any decrease in bone formation is not known, but this would further increase the negative bone balance.

The classic sites for fracture in postmenopausal osteoporosis are the distal forearm, the vertebral bodies, and the neck of the femur. These three fractures have a combined incidence of 35-40% in women aged over 65,³² and their clinical consequences are devastating. Epidemiological studies conducted 18 years ago in white women showed that the fracture rate of the distal radius rises about 10-fold between the fifth and seventh decades, reaching about 50 per 10 000 women annually at the latter time.^{1 2} Over the age of 60, 25% of white women have radiological evidence of vertebral crush fractures,³³ which contribute to loss of body height and may progress to extreme spinal flexion kyphosis. In terms of morbidity, mortality, and cost, however, the consequences of fracture of the proximal femur are even more important. By the late 1970s fracture of the neck of the femur ranked third in the list of use of non-psychiatric beds in England and Wales,³⁴ and calculations from Hospital In-Patient Inquiry data³⁵ show that 31 618 women aged over 45 were admitted with this diagnosis during 1977. The mortality in hospital, 16.8%, was about 20 times that expected for a population of this age. Admissions for men, in whom this fracture probably represents the end stage of senile osteoporosis, amounted to only 7674. We believe the reason for the sex discrepancy in the age-specific fracture rates of the proximal femur is postmenopausal osteoporosis. The number of bed-days used by this disorder in 1977 was 677 597, which represents occupation of 10% of all orthopaedic and traumatology beds at a cost, by 1981 figures, of roughly £48m (A Fenton Lewis, personal communication). This drain on hospital resources can only increase if current trends continue. For reasons that are incompletely understood, but cannot be fully explained by population growth, the incidence of fracture of the neck of the femur has risen sharply in recent years, and the overall increase in bed use between 1968 and 1977 was 48%.³⁵ To this must be added the consequences of fractures of the wrist and spine, which in total are devastating for both the postmenopausal population and the resources of the National Health Service.

Similar data are available from the United States. About 125 000 fractures of the proximal femur occurred in older women in 1979,³⁶ with estimated costs in excess of one billion dollars. Over 80% of fatal hip fractures occur in postmenopausal women, and each year at least 15 000 women are thought to die as a result.³⁷

If fractures are to be prevented osteoporosis must be diagnosed as early as possible to enable treatment to be given promptly. Unfortunately, bone rarefaction becomes apparent on a plain radiograph only when one-third of the skeletal mass has been lost. Measurement of trabecular bone volume in iliac crest biopsy specimens permits the early diagnosis of osteoporosis, but the invasive nature of this technique renders it unsuitable for screening large numbers or for long-term follow-up. Photon absorptiometry is one of the most accurate non-invasive methods for determining skeletal mass, but the cost of the equipment will restrict it to specialist centres for the foreseeable future. Furthermore, it measures bone density in the peripheral skeleton, which (like the iliac crest trabecular bone volume) does not correlate particularly well with spinal bone density.³⁸ One measurement which assesses the mineral content of spinal bone is estimation of the total body calcium by neutron-activation analysis, but again this will not become generally available because of the specialised facilities and

equipment needed. Newer techniques requiring further evaluation include dual-photon absorptiometry³⁹ and computed tomography scanning of the vertebrae,⁴⁰ while more generally available techniques such as radiograph morphometry have many shortcomings.³⁸ Thus most clinicians will still have to rely on assessments of plain radiographs of the lateral spine for diagnosis and follow-up.

Having made the diagnosis of osteoporosis the crucial decision for the doctor is whether symptomatic treatment is all that is required or whether treatment should be started to prevent further loss of bone mass. At present the end stages of the disease, severe generalised osteoporosis or fractures, or both, are treated mainly by physicians, general practitioners, physiotherapists, and orthopaedic surgeons, who concentrate on relieving pain and restoring and then maintaining mobility, however limited. Should these patients be given additional treatment aimed at conserving bone mass?

No treatment available can restore bone mass to normal, so any successes from this approach must be limited in patients with severe postmenopausal osteoporosis. Furthermore, if any increase in bone mass is to be achieved many years of treatment may be required, and thus the age and life expectancy of the patient must be taken into account. On balance, therefore, such treatment is unlikely to benefit severely affected women aged 70 or older. Nevertheless, further loss of bone mass may be prevented even when some years have elapsed since the menopause, and so we believe that a different approach is warranted in younger patients with osteoporosis (aged under 65), who should be treated actively. Such treatment should also be seriously considered in older women without or with only one or two fractures.

Clearly prevention of postmenopausal osteoporosis would be the ideal management but this requires a means of selecting the subpopulation of women at greatest risk. Treatment is mandatory after premature ovarian failure or castration, when it will prevent the early development of osteoporosis.⁴¹ There is, however, no clear-cut method of identifying women most at risk of developing osteoporosis after natural menopause, though measurements of circulating oestrogen⁴² and calcitonin⁴³ concentrations may give some indications. A reliable and widely applicable method of identifying women at risk is urgently needed.

Given that the doctor has decided that active treatment is indicated, one must be chosen which is effective. The responses to the various treatments that have been evaluated support our concept of the pathogenesis of postmenopausal osteoporosis. Oestrogen is the optimum treatment and its effectiveness is undoubted in preventing both loss of bone¹⁰⁻¹⁵ and fractures.^{14 18-20} The optimal duration of treatment remains to be determined, but oestrogens not only conserve bone mass when first started some years after the menopause but are effective in the long term.¹⁴ Recent data show that loss of bone is not accelerated after withdrawal of treatment,¹⁵ as was believed,^{16 18} and thus several years of treatment given shortly after the menopause may give lasting protection to the skeleton. Clearly early loss of ovarian function requires a longer duration of treatment.

Surprisingly, many other forms of treatment are still prescribed despite the lack of convincing evidence of any beneficial effect. The most comprehensive studies on the treatment of postmenopausal bone loss have reaffirmed the protective effects of oestrogens, and have conclusively shown that fluoride and various vitamin D metabolites are, as might be expected, of little or no benefit.^{12 44} These studies also showed that bone loss was not prevented by dietary calcium

supplements. This finding is supported by another study¹¹ which reported that large oral doses of calcium were unable to prevent bone loss to any great extent: calcium supplementation had only a small beneficial effect on the loss of ulnar bone and none on that of the radius. Though undoubtedly the diet should be adequate in minerals and vitamins, there is no convincing evidence that calcium supplements alone are an adequate treatment for postmenopausal bone loss as assessed by direct measurements of skeletal mass.

In our opinion, the risks of oestrogen treatment have been overstated. The incidence of thromboembolic events in postmenopausal women taking natural oestrogens is not increased,⁴⁵⁻⁴⁸ and the risk of developing endometrial hyperplasia and carcinoma may be kept to a minimum by adding a progestogen.⁴⁹⁻⁵¹ Incorporation of a progestogen may confer additional but previously unsuspected benefits on bone state. The two prospective, controlled studies which have evaluated combined oestrogen-progestogen regimens both showed an increase in bone mass when treatment was started within three years of the menopause, and this beneficial response was maintained for the duration of treatment, three¹⁵ and 10 years⁵² respectively.

There will always be some postmenopausal women in whom oestrogens are contraindicated. What treatment should these women receive? Theoretically, calcitonin should be of benefit, and recent reports suggest that this might be so,⁵³⁻⁵⁵ but further studies are necessary to establish a place for calcitonin in the overall management of postmenopausal osteoporosis. In such women the risks of oestrogen administration will have to be weighed against the sequelae of osteoporosis in terms of morbidity and mortality until an effective alternative has been definitely established.

Many fundamental questions about the management of postmenopausal osteoporosis still need to be answered. In general, however, undoubtedly the condition is managed too conservatively. Furthermore, though oestrogen is the only established treatment it appears to be overlooked by many clinicians.⁵⁶ Until these prevailing attitudes change, the appalling consequences of postmenopausal bone loss in women seem likely to continue undiminished.

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