Dr C Jasani, Dr B E C Nordin, Dr D A Smith and Dr I Swanson
(University Department of Medicine, Glasgow, and MRC Mineral Metabolism Unit, Leeds)

Spinal Osteoporosis and the Menopause

Although osteoporosis was distinguished histologically from osteomalacia in 1885 by Pommer, it remained a rather obscure disorder until Albright and his colleagues described it as a clinical entity in 1941. In their first series of 44 cases below the age of 64, no fewer than 40 were post-menopausal women and 10 had undergone an artificial menopause. For this reason they attributed the condition to gonadal insufficiency resulting in a reduced rate of synthesis of bone collagen.

It has always been a matter of common observation that spinal osteoporosis occurs most frequently in post-menopausal women, but it is also extremely common in the elderly of both sexes and the distinction between the so-called post-menopausal and senile varieties has never been clarified. Moreover, recent work (reviewed by Nordin 1964) has demonstrated that increased bone resorption rather than decreased bone formation is the likely cause of the condition and this has cast doubt on the collagen theory of osteoporosis and so on the role of the gonadal hormones as well. This doubt has been accentuated by the absence of convincing evidence that osteoporosis responds to treatment with gonadal hormones.

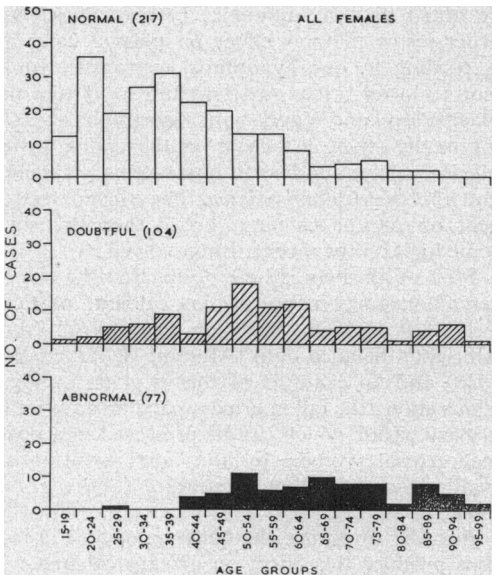

Fig 1 *Frequency distribution histograms of normal, doubtful and osteoporotic X-rays among 398 films examined in various countries without prior knowledge of the patient's age or sex. Note the onset of osteoporosis in the fifth decade*

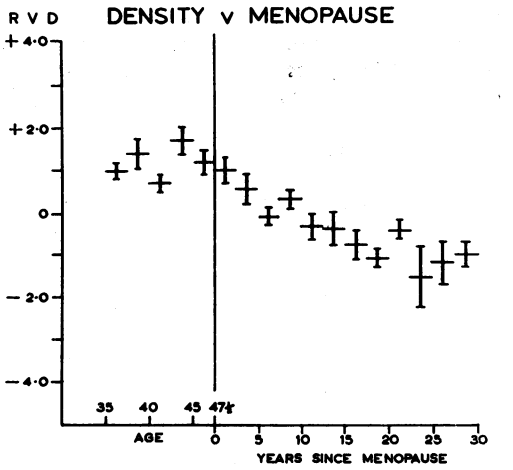

Fig 2 *Relative vertebral densities of 152 normal women surveyed in Glasgow. The vertical lines embrace two standard errors either side of the mean. Note the fall in density which starts after the menopause*

The role of the menopause in the pathogenesis of spinal osteoporosis has none the less continued to attract attention and evidence has accumulated that the disorder commonly starts in women between the ages of 45 and 50. Thus Saville (quoted by Bronner 1962) found that the specific gravity of iliac crest bone obtained from random autopsies started to fall in women at this age. In males, the specific gravity started to fall somewhat later.

One of us (B E C N) recently visited a number of countries of Europe, Asia, Africa and America and examined spinal X-ray films for evidence of osteoporosis. The films were classified as normal, doubtful or osteoporotic without knowledge of the patient's age or sex. Subsequent analysis of the data from 781 films showed not only that the proportion of abnormal films rose with age but that in women this rise could be dated quite clearly from the second half of the fifth decade (Fig 1).

This indication that, in many different countries, spinal osteoporosis starts at the menopause in women is supported by a survey of normal women which we have recently completed in Glasgow. In this study, lumbar spine densitometry according to the technique of Nordin *et al.* (1962) was carried out on 152 normal women. It was found that spinal density remained steady until the early 50s and then showed a sharp and significant fall (Fig 2) followed by a much slower fall thereafter. X-ray measurements of the hands and femur (Barnett & Nordin 1960) showed that

metacarpal cortical thickness fell about ten years after the menopause and femoral cortical thickness about five years later. Vertebral biconcavity did not appear at any age in this normal population.

Thus it looks as though some degree of 'osteoporosis' is a common phenomenon in women after the menopause – we cannot yet say whether it also occurs in men. At what stage this process becomes pathological or whether indeed the pathological form of osteoporosis is simply an accentuation of a normal process or a different condition altogether we do not know. But the striking rise in the incidence of Colles' fracture in women after the menopause which has been noted by Buhr & Cooke (1959) and by Alffram (1964) contrasts with the parallel rise in femoral neck fracture in men and women after the age of 70 and almost suggests that senile osteoporosis is not the same condition as the post-menopausal variety.

These data focus attention on the menopause and therefore on the effects of the œstrogenic hormones on calcium metabolism. Clearly, the diminution in bone volume which characterizes osteoporosis must be associated with a negative calcium balance, but the problem is whether the negative calcium balance is secondary to a primary rise in bone resorption or the rise in bone resorption is the result of an external negative calcium balance (Nordin 1960, 1961). One way of distinguishing between them might be the careful measurement of plasma calcium. Thus, if the loss of œstrogenic activity has a direct effect upon bone resorption and increases the release of calcium into the plasma, it will tend to raise the plasma calcium and so also the urinary calcium.

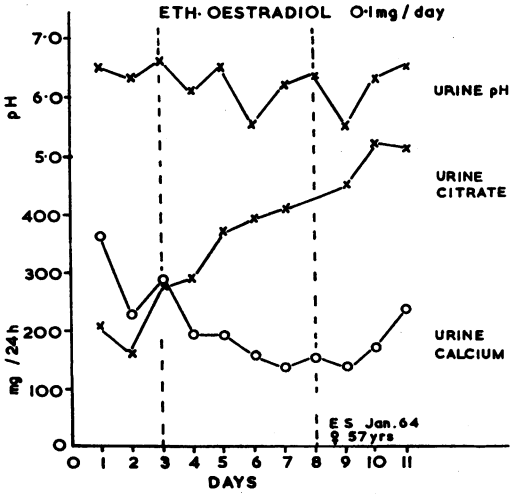

Fig 3 *Effect of ethinyl œstradiol on urine pH, urine citrate and urine calcium in a post-menopausal woman*

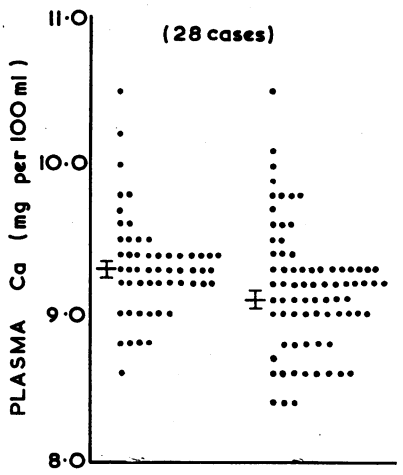

Fig 4 *Effect of ethinyl œstradiol 0·1 mg b.d. on plasma calcium in 28 subjects. The horizontal bars embrace one standard error either side of the mean and the difference between the means is significant* ($t = 2{\cdot}0$, $P < 0.05$)

If on the other hand œstrogens tend to increase either the renal tubular reabsorption of calcium or the absorption of calcium from the small intestine (or both) then deficiency of œstrogenic hormones (unless associated with an increased calcium intake) would tend to lower the plasma calcium and consequently increase the rate of bone resorption in order to maintain the plasma level. It will be noted that the difference between these two processes is in their effect on plasma calcium. According to one hypothesis, œstrogens would tend to lower urinary calcium and so to raise the plasma level and reduce bone resorption; according to the other, œstrogens would tend to lower plasma calcium and so to lower urinary calcium and improve calcium balance. The effect of œstrogens on plasma calcium should therefore shed some light on the mechanism involved.

First of all there is little doubt that the œstrogenic hormones reduce urinary calcium, particularly if it is high. This can be inferred from Albright's balance data (Albright & Reifenstein 1948) and an example of this is given in Fig 3 which shows the fall in urinary calcium and rise in urinary citrate which can be produced in a post-menopausal woman by the administration of small doses of ethinyl œstradiol (Shorr *et al.* 1942).

In order to pursue the question of how œstrogens produce this effect on urinary calcium, we have examined their action on plasma calcium, having already shown, with the help of the Auto-Analyser, that the effect of low calcium diets on urinary calcium is mediated through very small changes in plasma calcium (MacFadyen *et al.*

1965). Preliminary results in this study are shown in Fig 4 based on observations on 28 cases of osteoporosis and renal stone disease. The procedure was to measure the plasma calcium at 9.0 a.m. on one or two days before giving œstrogens and then to administer ethinyl œstradiol 0·1 mg b.d. and measure the plasma calcium daily at the same time, for three to ten days. In those cases in which plasma calcium was measured by flame photometry no significant change in plasma calcium occurred, but in the 28 cases in which it was measured by the Auto-Analyser there was a significant fall in plasma calcium. Although these results are only preliminary, they do at least suggest that the œstrogens do not raise the plasma calcium and make it unlikely that they act primarily on gut or kidney.

If the œstrogens tend to depress plasma calcium (and so urinary calcium) it seems legitimate to speculate that the menopause may be associated with a slight rise in plasma and urinary calcium. There remain, however, at least two ways in which this might occur. On the one hand, the increase in bone resorption could be, as it were, a primary effect of the hormonal deficiency on bone itself, in which case the resulting negative calcium balance would simply be a manifestation of the disease and presumably unaffected by calcium intake. On the other hand, œstrogens might have an effect on the blood/bone equilibrium antagonistic (directly or indirectly) to that of the parathyroid hormone in which case their effect on the body's calcium economy would operate through their effect on plasma and urinary calcium. This would also mean that the post-menopausal woman tended to maintain a higher plasma calcium than the pre-menopausal one but in this case the resulting negative calcium balance (due to hypercalciuria) would be reversible if the calcium intake were raised. Thus it should be possible to take the investigation a stage further if one could establish the effect of high calcium intake on bone resorption in osteoporosis.

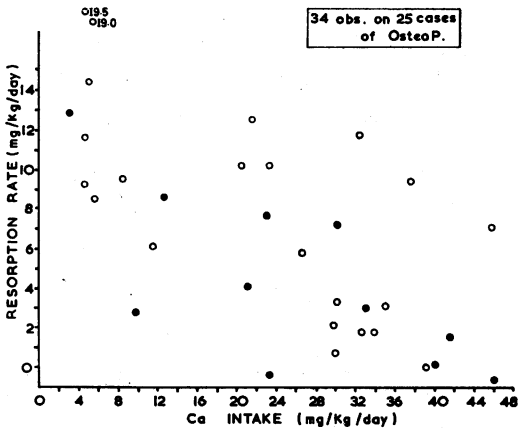

Fig 5 *Relation between calcium intake and bone resorption rate (each expressed in mg/kg per day) in 25 cases of osteoporosis. One highly negative resorption rate must be in error. Generally there is a fall in resorption rate with increased calcium intake (solid dots based on Nordin* et al. *1963 and open circles on Nordin* et al. *1964)*

There are at least two ways of measuring bone resorption. The first is by means of radioisotopes, which can in turn be used in two ways. Thus one can measure bone formation rate and calcium balance simultaneously and estimate resorption rate from the difference between them. We have done this in 25 cases of osteoporosis with the result shown in Fig 5, which indicates that resorption is inversely related to calcium intake. The second method is to feed the isotope continuously and determine the resorption rate from the difference between the dietary and plasma specific activity (Nordin *et al.* 1964). We have done this in 13 cases of osteoporosis and found that the plasma/dietary specific activity ratio is reduced by raising the calcium intake, indicating that a high calcium diet inhibits bone resorption (Fig 6).

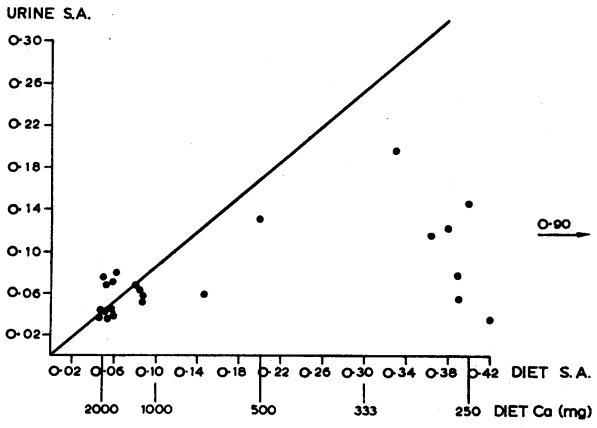

Fig 6 *Relation between dietary and urinary specific activity in 24 balance studies on 13 cases of osteoporosis. Note that when the dietary calcium is high, the urinary and dietary specific activities are equal indicating inhibition of bone resorption*

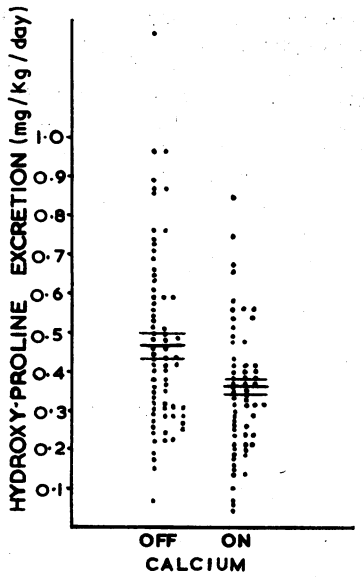

Fig 7 *Urinary hydroxyproline excretion in 73 cases of osteoporosis untreated and in 64 on calcium glycerophosphate supplements. Fifty cases are common to both groups. The horizontal bars embrace one standard error either side of the mean and the differences between the two means is highly significant.*

The alternative method of estimating bone resorption rate is by determining the excretion of hydroxyproline in the urine since hydroxyproline comes from collagen breakdown and bone contributes at least half of the amount appearing in the urine. Both we (Smith & Nordin 1964) and Klein *et al.* (1964) have shown that the rate of urinary hydroxyproline excretion is correlated with the bone resorption rate. We have therefore measured urinary hydroxyproline in 72 cases of osteoporosis on their home diets and in 63 cases on calcium supplements (50 cases being common to the two groups) and found the highly significant fall in hydroxyproline output shown in Fig 7.

From these observations we conclude that the increased bone destruction which leads to osteoporosis is secondary to negative calcium balance rather than vice versa.

As a working hypothesis, we therefore suggest that the œstrogenic hormones have an action on the blood/bone equilibrium antagonistic to that of the parathyroid hormone (as suggested by the work of Ranney 1959) and that a reduction in œstrogenic activity leads to a marginal elevation of plasma calcium and so to hypercalciuria and to negative calcium balance. The degree of osteoporosis which this produces must depend upon the length of time which elapses before the subject re-adapts to the new situation. Since the sites of bone loss appear to be highly selective, a negative balance of only 50 mg daily for five years (15–20 g calcium) would be sufficient to destroy a significant amount of trabecular bone.

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