THE PROBLEM OF OSTEOPOROSIS

Critical Review

RUSSELL FRASER, LONDON, ENGLAND

From the Department of Medicine, Postgraduate Medical School of London

Fracture of the neck of the femur is an injury often sustained by elderly women, and recent epidemiological surveys have suggested that osteoporosis may be an important predisposing factor. The problem of osteoporosis therefore compels our attention, though it must be admitted that we still do not understand all the important points. Long ago Pommer (1885) recognised osteoporosis or "simple atrophy" of bone. He distinguished it from osteomalacia, the condition in which defective calcification of the skeleton is shown by excess of osteoid tissue often arising from lack of vitamin D (Figs. 1 to 3). Unfortunately, the term osteoporosis has been used loosely to mean thinning of bone as shown in radiographs no matter what the cause, and it has been suggested that we call it "osteopenia." This means no more than that there is too little bone or bone atrophy, and not until we know more of the pathological changes can such a new term be justified. We should still use the old term osteoporosis, at the same time adhering to the precise meaning given to it by Albright, a disease characterised by atrophy of bone—that is to say, the bone is qualitatively normal but there is too little of it.

The final court of reference must clearly be based on histological examination. The diagnosis of osteoporosis is usually reached on radiographic evidence of thinning of bone when biochemical tests have excluded other possible causes. The conditions which in radiographic appearance may simulate osteoporosis can usually be revealed by examination of the blood chemistry, but in doubtful cases bone biopsy may be needed. Osteomalacia, hyperparathyroidism, uraemic osteodystrophy and malignant disease of bone such as myeloma must be excluded. In osteoporosis the rarefaction of bone is usually most evident in the axial skeleton, but the peripheral bones may also be affected. Barnett and Nordin (1960) suggested that the condition might be divided into two types—peripheral and central—but this suggestion awaits more certain proof. Moreover, although individual bones may show diffuse rarefaction, in more severe cases there is often a patchy character of bone change with radiographic evidence of lacunae.

STUDIES OF THE CAUSE OF OSTEOPOROSIS

Albright and Reifenstein (1948) in developing biochemical methods for the assessment of patients with bone disease were unable to find in osteoporosis any disorder of calcium and phosphorus metabolism, and suggested that the disease depended on defective growth of bone matrix. With the development of tracer methods it has become possible to check this hypothesis; and several observers have obtained results which do not seem to confirm it (Fig. 9). Closer scrutiny is showing that the interpretation of data gained by tracer methods is also difficult and may not yet be final. Such tracer observations have reopened the original hypothesis of calcium deficiency as the cause of osteoporosis (Pommer 1925, Nordin 1960). Meanwhile the treatment of osteoporosis has remained a problem (Henneman and Wallach 1957) whether by androgens or oestrogens as suggested by Albright and Reifenstein (1948), or by calcium supplements; and it is even more difficult to assess the efficacy of these treatments. For such an assessment we need to be able to measure bone density by radiographic methods and so to demonstrate reformation of bone during the period of treatment. Some methods of radiological assessment of bone density have now been evolved (Doyle 1961) so that we can expect a more careful appraisal of the various methods of treatment of osteoporosis.
Undecalcified sections of rat humeri showing in Figure 1 a normal control, in Figure 2 the effect of a low calcium diet, and in Figure 3 the effect of a similarly low calcium diet but also with deficiency of vitamin D. Note the loss of bone on a low calcium diet, but also the excessive loss of osteoid borders of osteomalacia when the diet is also deficient in vitamin D (von Kossa and van Gieson, ×90.) (With acknowledgment to the Journal of Endocrinology, 1960, 21, 197.)
THE PROBLEM OF OSTEOPOOROSIS

THREE CLINICAL GROUPS OF PATIENTS WITH OSTEOPOOROSIS

Clinically it is useful to distinguish three groups of patients with osteoporosis which might be described as complicated, atypical and typical. In the first group are the rare cases of osteoporosis arising as a complication of metabolic disorder such as Cushing's disease, thyrotoxicosis or acromegaly. The second or atypical group includes unusual cases of osteoporosis in young or middle-aged patients with no evidence of an associated metabolic disorder—so-called "idiopathic osteoporosis." The third group of patients comprises those that we see so often, especially women, with post-menopausal or senile osteoporosis.

Osteoporosis as a complication of metabolic disease—In these patients the osteoporosis is part of a wider picture of metabolic disorder such as acromegaly, Cushing's syndrome or thyrotoxicosis. They are made clear from other types of osteoporosis by the associated clinical

<p>| TABLE I |
| SUMMARY OF INVESTIGATIONS IN CASE OF ACROMEGALY BEFORE AND AFTER 131I IMPANTATION (HARRISON, JOPLIN, HARTOG AND FRASER 1960) |</p>
<table>
<thead>
<tr>
<th>Pre-implant (October 1959)</th>
<th>Three months post-implant (January 1960)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand volumes (right left: millilitre)</td>
<td>635/605</td>
</tr>
<tr>
<td>Insulin tolerance test: (11.1 units S.I./square metre). Sum of blood sugars at 60, 90 and 120 minutes. (Normal less than 135)</td>
<td>189 (Resistant)</td>
</tr>
<tr>
<td>Prednisone load test: change in overnight urinary sugar after 20 milligrams at noon, 4 p.m., 8 p.m. (Normal less than 50 milligrams/hour)</td>
<td>29→366</td>
</tr>
<tr>
<td>Urinary calcium (milligrams/24 hours) on 550 milligrams/day intake. (Normal less than 200)</td>
<td>300</td>
</tr>
<tr>
<td>Sr test for exchangeable calcium. (Normal 8 to 18 plasma units)</td>
<td>17.3</td>
</tr>
<tr>
<td>Daily deposition of calcium. (Normal 1.0 to 2.0 plasma units)</td>
<td>2.4</td>
</tr>
<tr>
<td>Plasma citrate (milligrams per cent). (Normal 1.5 to 3.0)</td>
<td>5.50</td>
</tr>
</tbody>
</table>

signs of the primary disease—obesity, amenorrhoea, hypertension, bruising of tissues, plethora and so on. The osteoporosis responds only to correcting the primary metabolic disorder. For example, treatment of Cushing's disease nearly always relieves the aching pain in bones and the susceptibility to fractures, and lessens the osteoporosis. Yet, except in children (Figs. 4 to 6) the bones seldom regain normal density, and this may be very significant in considering typical osteoporosis of the post-menopausal and senile type. Osteoporosis is probably lessened when its cause is removed, but only enough to minimise the risk of fracture and not enough to show much improvement on radiographic examination. It is clear that, once there is severe osteoporosis, normal bone structure cannot easily be restored. It is important to study these complicated or secondary types of osteoporosis for the important lessons that they may offer for the commoner problems of typical osteoporosis.

Acromegaly—Albright had many theories to explain the osteoporosis which develops in acromegaly with kyphosis. Although none of these theories seemed to ring true, our knowledge of the action of growth hormone at that time could offer nothing better. Despite the early discovery of the potency of pituitary growth-hormone in rats (Evans and Long 1921) fuller studies in man were delayed until it was found that only human or monkey growth-hormone was potent in man (Raben 1959). Hypercalcemia was shown to be one of the striking effects of injecting human growth-hormone in man (Fig. 7). We can reasonably assume that the osteoporosis of acromegaly depends on this same action (Fraser and Harrison 1960). It is
Girl aged twelve years with Cushing's disease before and after treatment with pituitary 
\(^{198}\)Au implant (Figs. 5 and 6). Bone density measurements of the ulna by Doyle's method 
are shown in Figure 4. Note the original osteoporosis and improvement after treatment. 
With acknowledgment to the *British Journal of Radiology*, 1961, 34, 407.)
striking that when acromegaly is treated effectively, as for example by implantation of radioactive gold, \(^{198}\text{Au}\), into the pituitary (Table I), the hypercalcuria is corrected without alteration of the serum calcium or phosphorus levels (Harrison, Joplin, Hartog and Fraser 1960). It was at first thought that growth-hormone must increase the concentration of circulating citrate and thereby increase the filterability of calcium into the urine by its chelating action. When this was studied in rats (Karam, Harrison, Hartog and Fraser 1961) a different

\[
\text{MEAN CHANGES IN URINE} \quad \begin{array}{c|c|c|c}
\text{Nitrogen} & \text{Calcium} & \text{Sodium} & \text{Potassium} \\
\hline
\text{AFTER 30mg H.G.H.} & \text{1.4 hypopituitary patients} \\
\end{array}
\]

The acute effects of injecting human growth hormone into hypopituitary patients. Note the prolonged rise in the urinary output of calcium, along with the more familiar nitrogen retention. (From Lancet, 1959, i, 7.)

but interesting connection between the hypercalcuria of growth-hormone and the metabolism of citrate was established. Growth-hormone was found to lower the citrate levels in renal tissue and so to lower renal reabsorption of calcium, thereby impairing the body's conservation of calcium (Fig. 8). In confirmation, the opposite effect, a lowering of urinary excretion, was observed when tissue-citrate was raised by fluoro-acetate poisoning (Karam et al. 1961). Quite possibly this hypercalcuric action of growth-hormone is seen only when its production is greatly increased. There is, however, a hint here that we must look into conditions affecting the metabolism of intermediates such as citrate in seeking the causes of osteoporosis. 

Cushing's syndrome—Orthopaedic surgeons do not need to be reminded that over-production of cortisol as in Cushing's disease, or excessive administration of cortisone or its substitutes in treatment, may cause osteoporosis. It cannot be emphasised too much that the most important treatment is to prevent the over-production and avoid the over-administration of corticosteroid. Much can be done along these lines. At the same time there must be an adequate diet, especially regarding protein and calcium, both of which are well supplied in dairy products, together with androgens or other anabolic agents.

The mechanism of this osteoporosis is not clearly established. When Cushing's syndrome affects children their growth is retarded, as is also the healing of cuts and fractures at any age. Whether bone growth is especially defective is hard to say. As some confirmation of the importance of defective growth in causing the osteoporosis of Cushing's disease we should note that this is the one type of osteoporosis in which calcium tracer tests show defective deposition of calcium in bone (Fraser, Harrison and Ibbertson 1960). While bone growth is defective, bone resorption proceeds with undiminished and possibly enhanced speed (Fig. 9).
The exact mechanism by which an excess of corticosteroids impairs growth and causes osteoporosis still awaits elucidation. One factor is undoubtedly their tendency to deviate protein metabolism away from growth and towards gluco-neogenesis, or fat and sugar production. Their effect on metabolic intermediates in doing this may also be an important factor in causing osteoporosis.

**Thyrotoxicosis**—A striking example of osteoporosis is occasionally produced, probably by a different means, in thyrotoxicosis. In contrast with Cushing's disease, thyrotoxicosis in children leads to excessive growth; so the mechanism must be different. A notable feature in thyrotoxicosis is the tendency to rapid turnover of calcium by the bones and to excessive calcium loss in the urine and faeces. Whatever its mechanism, this calcium diarrhoea is probably an important factor in causing osteoporosis. Fortunately, most patients with thyrotoxicosis have suitable treatment long before the osteoporosis becomes a serious clinical problem.

**Atypical osteoporosis**—One of the difficult problems in osteoporosis is the occasional rare case of osteoporosis in a young child or adult in whom no associated metabolic abnormality such as Cushing's disease can be discerned (Berglund and Lindquist 1960). These cases of "idiopathic osteoporosis" are at present a challenge to discovery, and we can only apply our knowledge of physiology to try and limit their advance. It could be that these are subjects who have a defective ability to form bone, analogous to the disorder in osteogenesis imperfecta; but it also could be that they suffer from some undiscovered metabolic disorder interfering with bone formation and growth. These children do not grow. Similarly calcium-deprived rats which are otherwise normal do not grow (Harrison and Fraser 1960a). Various other types of atypical osteoporosis may be found in these younger patients which

![Fig. 8](image_url)

**Fig. 8**

Growth hormone raises urinary calcium probably by lowering renal citrate. (From Clinical Science, 1961, 21, 265.)

![Fig. 9](image_url)

**Fig. 9**

Tracer measurements of rate of calcium deposition in bone in osteoporosis, measured with stable strontium. Note that most results are in the normal range. (CaE equals exchangeable calcium; and CaB daily bone deposit of calcium; both in total plasma calcium units, described by Fraser et al. 1960.)
THE PROBLEM OF OSTEOPOROSIS

are not yet understood—chronic jaundice (Atkinson, Nordin and Sherlock 1956), urticaria pigmentosa and post-pregnancy osteoporosis.

**Typical osteoporosis**—Under this title we group together the uncomplicated osteoporosis seen all too often in post-menopausal and senile subjects. The cause is still a mystery. The problem is dominantly one of women, affecting them at an earlier age than men, probably not because it is truly post-menopausal as suggested by Donaldson and Nassim (1954) from their observations on surgical menopause. Primarily it involves the axial skeleton, though in more severe cases it involves all bones. Unfortunately bone-density measurements are practicable only on the peripheral skeleton, and it is not yet certain how far this discloses the extent of the disorder. It may be hoped that this question will be studied on post-mortem material.

Our knowledge of the patho-physiology of this condition is unfortunately based on probabilities. Serum-calcium and phosphorus levels are normal unless there is the complicating factor of prolonged immobilisation; and this feature is of course of diagnostic importance. However, the bones have atrophied and so there must have been a negative calcium balance at some time when the disease was developing, though we seldom know the basis. We do not know whether in typical cases of osteoporosis this was due to excessive resorption, defective deposition of bone, or both, though the present evidence tends to emphasise the first. We do know that when osteoporosis occurs from long immobilisation in plaster the bone appears to waste away from excessive resorption (Engström and Amprino 1950).

**CALCULUM TRACER STUDIES**

Calcium tracer studies do not agree in their assessment of the rate of bone deposition in osteoporosis. Most seem to indicate normal rates of bone deposition of calcium (Harrison *et al.* 1960, Heaney and Whedon 1958) while others show slightly decreased deposition rates, perhaps because they have been compared against tests on athletic young subjects (Eisenberg and Gordan 1961). In any case, with the thin bones of osteoporosis, merely normal rates of calcium deposition may imply inadequacy in the rate of bone formation (Fig. 9). Before the development of these tracer methods, osteoporosis was attributed to defective osteogenesis because there was no definite evidence of excessive bone resorption. In the flush of these new methods there has perhaps been a too rapid assumption that their measurement of the rate of disappearance of tracer into the bone reflects the rate of new bone formation. Along with new bone formation, calcium ions also enter bone in the steady process of exchange which has generally been assumed to alter in disease in parallel with the rate of new bone formation. If this critical assumption is wrong (Fraser *et al.* 1960), the results of these tracer measurements in osteoporosis might need setting aside until we can distinguish between the fraction of calcium moving into bone from exchange, and that reflecting new bone formation. As yet there is no clear lead on how to do this.

**CALCULUM DEFICIENCY AS A POSSIBLE CAUSE OF OSTEOPOROSIS**

Recently, as the therapeutic value of oestrogens and androgens in the treatment of osteoporosis has been shown to be so doubtful (Henneman and Wallach 1957), the calcium-deficiency hypothesis has been revived. It is quite clear that in experimental animals calcium-deficiency without vitamin D deficiency leads to osteoporosis and not to osteomalacia (Figs. 1 to 3), and sometimes in human subjects this has been established as the basis of osteoporosis. Clearly a negative calcium balance whether from defective diet, defective absorption or excessive urinary loss could lead to osteoporosis; but it would also be a feature of the disease whatever its cause, as for example in Cushing's disease. This raises the question whether a chronic negative calcium balance might be a common background to this and to post-menopausal and senile osteoporosis. It has been discussed by Nordin (1960) and others,
Calcium balances in normal, post-menopausal or senile osteoporotic and miscellaneous other osteoporotic subjects on medium calcium intake (0.33 m.eq. kg/day). Note no difference between groups. (From Lancet, 1961, i, 1,015.)

Change in net absorption and in urinary calcium immediately after the establishment of a high calcium intake (2 m.eq./kg./day) preceded by a medium calcium intake (0.33 m.eq. kg. day). (From Lancet, 1961, i, 1,015.)

Total external calcium balance first on a medium calcium intake (0.33 m.eq. kg. day) and then immediately after instituting high calcium intake (2 m.eq. kg./day) in osteoporotic subjects. Note on moving to high calcium diet the normal subjects develop a moderately positive Ca balance, but most of the osteoporotic subjects develop a more strongly positive Ca balance. (From Lancet, 1961, i, 1,015.)
but proof or disproof is difficult. Malm (1958) has shown that with careful balance studies some subjects have a poor capacity to adapt to low calcium intakes, and they may be the ones who readily develop osteoporosis when the calcium intake is marginal. This theory is still being assessed. Bone density measurements are only just becoming adequate, but they will be crucial in assessing the therapeutic tests of such a theory. Moreover, very precise measurements are needed, for, as discussed in the next section, correction of the cause may only arrest and not cure the disease.

Important, though not final, evidence for the calcium deficiency hypothesis is that of careful balance studies. As an example we may examine the findings of Harrison, Fraser and Mullan (1961). A series of sixteen patients with typical but obvious osteoporosis (post-menopausal or senile osteoporosis with or without fractures, but without other clinically detectable complicating factors) were studied. They were contrasted with a similar number of normal subjects and some patients with atypical or “idiopathic” osteoporosis. Each

patient was studied for three weeks, first on a medium calcium intake (6-6 milligrams per kilogram) and then on a high calcium intake (40 milligrams per kilogram). As in previous studies, it was found that during the medium intake the calcium balance data of patients with osteoporosis did not differ from those of the normals (Fig. 10). But on moving to the high-calcium intake (Figs. 11 to 12) it was found that two-thirds of patients with typical osteoporosis showed an excessive absorption of calcium, suggesting that they could form bone in excess of the normal rate if offered enough calcium. Furthermore, prolonged observations over periods ranging from nine to forty-eight months showed the high-calcium diet to be still causing calcium retention in four of the six subjects receiving the calcium supplements. (From Lancet, 1961, i, 1,015.)

![Figure 13](image-url)

**FIG. 13**

The persistence in post-menopausal and senile osteoporotics of a positive calcium balance on a high (2 m.eq./kg./day) intake. Note prolonged positive calcium balance maintained in four of the six subjects receiving the calcium supplements.

Vol. 44, No. 3, August 1962
THE PROBLEM OF BONE GROWTH IN OSTEOPOROSIS

In studying calcium-deficiency osteoporosis in rats, Harrison and Fraser (1960a) found that avidity for calcium associated with this condition gradually declined with age (Fig. 14). Therefore, when we finally gave these deficient rats a high calcium diet, their osteoporosis could be corrected only if they were not too old. Elderly osteoporotic subjects might also need some aids such as androgens and oestrogens in addition to calcium to enable them to form more bone. Here we are reminded of the osteoporosis of Cushing's disease—of how it can be difficult to do more than arrest its progress by curing the Cushing's disease, except in young subjects. Our problem in typical osteoporosis must often be similar: not only how to remove the cause of the osteoporosis, but also how to stimulate regrowth of bone.

REFERENCES


