THE STUDY OF OSTEOPOROSIS AND OSTEOMALACIA

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ALTHOUGH many articles have appeared in the journals in recent years on the subjects of osteoporosis and osteomalacia, our knowledge of these subjects continues to be very fragmentary. In the case of osteoporosis there has been much controversy about the aetiology. Some continue to agree with the views of Albright and Reifenstein (1948) that osteoporosis is primarily due to abnormality of the bone matrix, while others have reverted to the earlier view that there is primarily a deficiency of calcium. The pros and cons of these two views have been reviewed recently (Lancet 1963) and need not be discussed in detail here. Others have considered the aetiology in quite different terms altogether. Thus, Little (1963) concluded, as a result of electron microscope studies, that the osteocytes of osteoporotic bone liberated a substance which degraded the matrix following which mineral was removed.

Treatment of Osteoporosis

With the aetiology of osteoporosis in doubt, it is not surprising that there is also doubt about the best treatment. The sex hormone treatment of Reifenstein and Albright (1947) now has the respectability of time. There seems to be no risk of carcinoma induction as was once feared and patients benefit from it (Henneman and Wallach, 1957) ceasing to lose height and to fracture. Positive calcium balances are not always seen, however, and often when seen are only slight in amounts, and the bones do not apparently remineralize (Henneman and Wallach, 1957; Nicholas and Wilson, 1959). The high calcium intake strongly recommended by Nordin (1962) is said to give the same symptomatic improvement and in addition to give strongly positive calcium balances. Nordin (1962) claimed positive calcium balances as great as 34 mg./kg. body weight (2.4 g. for a 70 kg. man) per day for periods of time of up to one year. Nevertheless no remineralization of bone has been demonstrated as yet even with this high calcium intake regime. This is puzzling because if a positive calcium balance of 2.4 g./day continued for a year then the total gain by the body would be 835 g., an amount which must be visible radiologically however distributed in the body. The normal adult skeleton contains 1,000–1,400 g. of

calcium (Albright and Reifenstein, 1948), and reduction of 30% to 50% can generally be detected by eye on an ordinary X-ray film (Lachman, 1955), so that a gain by osteoporotic bone of 835 g. could not be missed radiologically however diffusely this gain might be spread through the bones. Nordin himself has expressed some puzzlement writing (1962) 'It is perhaps surprising, even when this insensible loss of calcium (referring to sweat) is taken into account, that calcium supplements have not yet produced any convincing changes on spinal roentgenograms apart from some possible hardening of the end plates'. A possible explanation of this discrepancy between the radiological and the balance data is that the high calcium intake magnifies the errors inherent in the balance technique. Such seems quite likely when it is recalled that normally 80% of the ingested calcium appears in the stools, and that this figure becomes even higher on a high calcium intake, and yet complete stool collections are extremely difficult. Toilet paper is frequently rejected without analysis, small quantities of faeces may be lost in manipulation and even in the best-run metabolic units, stools may occasionally be lost without trace.

Although sex (and anabolic) hormones and high calcium intake probably represent the two therapies for osteoporosis in most common use at the present time, this by no means exhausts the list of therapies that have been recommended. It was claimed by Shorr and Carter (1952) that strontium salts given by mouth led to positive strontium balances after high calcium intake no longer gave positive calcium balances. This therapy was found to be effective by McCaslin and Jones (1959) but no balance data were given and the trial appeared to be uncontrolled. Albright and Reifenstein (1948) for the treatment of idiopathic osteoporosis. Again however this therapy does not appear to have been widely adopted. Anderson (1954) found that one patient with idiopathic osteoporosis repeatedly showed a striking fall in urinary calcium following each plasma infusion. Three other patients in the same series however failed to respond (Dent, 1955). Sodium fluoride therapy has recently been advocated for osteoporosis by Rich and Ensink (1961) who claimed

in a preliminary communication, that good positive calcium balances could be achieved. These results still await confirmation.

New Methods of Study

It therefore seemed reasonable to undertake new balance studies to try and compare the effectiveness of some of these various therapies in osteoporosis, and this is now in progress in this metabolic unit. Starting with the proposition that remineralization of bone is never seen whatever the therapy, it seemed likely that the changes in calcium balance to be observed might be small, so that a method of improving the accuracy of measurement of faecal calcium was required to avoid the possible errors discussed above. Two new methods have therefore been investigated. Firstly, the continuous chromium marking of stools of Whitby and Lang (1960) has been used. Rose (1964) has shown that the chromium sesquioxide follows the calcium and phosphorus in the stools remarkably closely so that losses of stools on toilet paper or in manipulation, or from any other cause, can be estimated and allowed for by measuring chromium recovery in the stools. The overall accuracy of the balance is therefore increased, and this will be true especially when faecal calcium is very high as on a high calcium intake. This fact is illustrated in Fig. 1 which shows the result of a 12-day balance study on an osteoporotic patient while in the fourth month of high calcium intake therapy. When faecal calcium is not corrected for chromium recovery, she appears to be in positive calcium balance of about 250 mg./day (in the range often claimed by others). But the chromium recovery was 89% and when allowance is made for the chromium loss the balance becomes virtually zero. Note that the chromium correction makes very little difference to the overall phosphorus balance since faecal phosphorus is so much less than the faecal calcium, both relatively and in absolute amounts.

The second method of improving measurement of faecal calcium is by the use of radioactive calcium. A tracer dose can be given orally and the recovery in the stools should indicate the extent of absorption of dietary calcium. By subtracting calcium absorbed from calcium given, the unabsorbed calcium is derived. Unabsorbed calcium differs from the faecal calcium by the calcium secreted into the bowel (but not re-absorbed). If this net secreted calcium is constant, then by assuming this value and knowing absorbed calcium (from the isotope study) one can calculate the actual faecal calcium. Others have attempted this before (see Eklund, 1962) but been unable to get the correlations expected. In conjunction with the Department of Medical Physics at

FIG. 1.—The calcium and phosphorus balance of an osteoporotic patient in the 4th month of high calcium intake. When the results are uncorrected for faecal chromium recovery, she appears to be in positive calcium balance of about 250 mg./day, but this is eliminated when the correction for lost chromium (and therefore lost faeces) is made.

In this and the other Figs. the balance data are constructed in the manner of Albright and Reifenstein (1948). Diet is plotted down from the zero line. From the diet line, excretion is plotted up, the shaded portion indicating faecal excretion and the clear portion the urinary excretion.

this hospital, this work is being repeated, using ^{47}Ca and using values for faecal calcium both with and without correction for chromium marker. Results obtained so far show greatly improved correlation when correction is made for chromium marker. These results are not yet complete however and will not be discussed further here.

Results in Osteoporosis

In this study of osteoporosis now in progress a repeated finding has been that the faecal calcium may be as high as, or higher than, the calcium intake, even though the intake has been normal and about the same as the patients' normal intake when at home. Patients may therefore be in negative calcium balance with an intake of about

FIG. 2.—Selected balance data from two studies on osteoporotic patients to show, firstly that the faecal calcium may equal or exceed the dietary calcium, even on a normal calcium intake, and secondly that the overall balance is not improved by lowering the faecal calcium with vitamin D. In each case, the fall in faecal calcium continued in the following 6-day period despite changes in therapy.

1 g./day and despite a normal or low urinary calcium, as shown in Fig. 2. Such high faecal calcium values have been observed before by others (Reifenstein and Albright, 1947; Lichwitz, de Seze, Paolaggi, Lanham, Hioco, Miravet and Bordier, 1962; Heaney, 1962) but have not been stressed, although the observation seems to have important theoretical and practical implications. Two possible explanations for the high faecal calcium present themselves. Firstly, it might be that the patient has an inability to absorb dietary calcium, and this gives rise to calcium deficiency which is the cause of the osteoporosis. If this were so then administration of vitamin D in sufficient dose to overcome the absorption defect should cure the condition. Fig. 2 shows that this does not occur since when the calcium is absorbed a positive calcium balance is prevented by a matching rise in urinary calcium. Note that in the case of Stella H. the rise in urinary calcium was preceded by the fall in faecal calcium (and this has been seen in another patient) so that it is most unlikely that the fall in faecal calcium was due to the rise in urinary calcium. A second explanation for the high faecal calcium therefore seems more likely, i.e. that the faecal calcium is actually maintained high because the bones cannot utilize the calcium. What the mechanism might be whereby this is achieved is interesting to consider, but no suggestions can be offered at the present time. The practical implication of the high faecal calcium concerns evaluation of the osteoporotic patient. Albright and Reifenstein (1948) considered that in post-menopausal osteo-

porosis, the urinary calcium was high during phase of demineralization of bone, and that later a normal or low urinary calcium indicated that a new calcium balance had been achieved and the aim in treatment was to lower the urinary calcium. This reliance on urinary calcium is clearly unwarranted when the faecal calcium is high, and it may be that in studying the effect of therapy it would be most unwise to ignore the faecal calcium and measure urinary calcium alone.

A second way of attempting to increase the dietary absorption of calcium is to raise the calcium intake without giving vitamin D. This has the advantage that it apparently does not cause the rise in urinary calcium which accompanies vitamin D therapy (see Fig. 2). Positive calcium balances have been obtained in the present study when the calcium intake has been raised from 1 to 3 g./day. But these positive balances have been observed only in the first 10 to 18 days of the treatment, and when patients have been sent out on the therapy and then been brought back for further balance study some 3 to 4 months later the positive balances have no longer been present. It seems that it has sometimes been possible to arrest a negative balance but never to establish a positive calcium balance for a long period. As already discussed above these results are at variance with those of Harrison, Fraser and Mullan (1961), and of Nordin (1962). At least three explanations are possible to explain this variance. Firstly, current methods of balance study seem to be more accurate than those avail-

able previously. Secondly, the calcium tablets formerly available (lactate or gluconate) were unpalatable when given in the large doses required and it seems likely that some patients would not take the full dose when sent home. By contrast, the calcium tablets used in this study have invariably been the Calcium-Sandoz effervescent tablets which make a pleasant drink which patients enjoy, so that it is much more likely that they will continue the treatment when at home and in between balance studies. Thirdly, we must not overlook the possibility that osteoporosis is not a single condition, and the patients studied in the present limited series may not have the same disease as those studied by others.

The evidence obtained so far in the present study is that no method of treatment used (high calcium intake, sex hormones, or fluoride) will put an osteoporotic patient into positive calcium balance for a prolonged period of time. It has been possible only to arrest a negative calcium balance. This has been achieved both with high calcium intake and by hormonal therapy, but fluoride therapy has as yet proved very ineffective. This is apparently a disappointing conclusion at which to arrive, but nevertheless it appears to be in accord with radiological evidence. Henneman and Wallach (1957) stated that 'careful review of radiographs made with standard technique after 5—20 years of estrogen therapy in this series has failed to demonstrate a single instance of increase in bone density'. Indeed very few workers have ever claimed to have shown remineralization of osteoporotic bone. When claims have been made (Martinez and Greenblatt, 1960) the evidence presented has been very unconvincing. Iannaccone, Gabrilove, Brahms and Soffer (1960) demonstrated that when the cause of osteoporosis in children was cured by surgical treatment of Cushing's syndrome, and when the new bone growth was then normal, even then the old vertebral bone did not remineralize. It therefore seems that remineralization of osteoporotic bone may be impossible, except perhaps in the case of acute immobilization osteoporosis.

This biochemical and radiological evidence against remineralization in no way gainsays the value of the treatment of osteoporosis in preventing further fractures and loss of height, since the arrest of a negative calcium balance may well be sufficient to achieve this. It does mean however that claims to have established prolonged and large calcium balances should be viewed with some caution.

Osteomalacia

The case for further studies of osteomalacia is a quite different one. Often, when osteomalacia is

treated, large changes in calcium balance can be produced and this can be done without recourse to a high calcium intake. Classical balance techniques were accurate enough to show these changes and it seems established that vitamin D-resistant osteomalacia (or rickets) can always be cured by giving a sufficiently large dose of vitamin D (with sodium bicarbonate as a second therapy if renal tubular acidosis is present). Dent and Harris (1956) however have pointed out that the resistance to the vitamin D applies only to the therapeutic effect and not to the toxic effects so that the therapeutic range may become very small. The therapy is therefore potentially hazardous, especially in chronic renal failure where hypercalcaemia may be especially disastrous (Dent, Harper and Philpot, 1961). Furthermore, the dose of vitamin D which may be needed to produce the positive calcium balance required to cure a patient may be toxic when the bones are fully recalcified so that the dose must be gradually and carefully lowered. If another therapy could be found which did not have these hazards it would be very advantageous. Another reason for seeking a different form of therapy is that sometimes the clinical response to vitamin D is unexpectedly slow. Fig. 3 shows the calcium balance of a patient with type 2 (Dent, 1952) renal tubular osteomalacia (hypophosphataemic osteomalacia plus a renal glycosuria). Vitamin D dramatically lowered the faecal calcium as was expected, but the overall improvement in calcium balance was very slight because of the rise in urinary calcium to very high levels. This patient was eventually cured with no other therapy, but it took many months of vitamin D therapy to get him walking again and heal the Looser zones.

Because of these hazards and difficulties which can occur in the treatment with vitamin D, other methods of treating osteomalacia are under investigation in this department. It was claimed by de Toni and Nordio (1959) that rickets, either of the classical D-deficient type or with vitamin D-resistance, could be cured by giving intramuscular injections of ATP without any vitamin D administration. X-rays were shown to support this claim but no balance data were shown. A calcium balance study was therefore carried out in Leeds in which a 7-year-old girl with type I (Dent, 1952) renal tubular rickets (hypophosphataemic rickets) was studied before and during ATP therapy as recommended by de Toni and Nordio. No improvement in calcium balance could be demonstrated after 12 days of this therapy and it was therefore abandoned and has not been attempted again. The girl subsequently did well on the usual vitamin D therapy.

FIG. 3.—The effect of vitamin D on the calcium balance of an osteomalacic patient. The plasma inorganic phosphate failed to rise to normal levels and this may be the reason why calcium absorbed from the intestinal canal has not been retained. Renal tubular acidosis was not present.

It was claimed by Fraser, Jaco, Yendt, Munn and Liu (1957) that intravenous phosphate infusions sufficient to restore the plasma inorganic phosphate to normal would cure rickets without the use of large doses of vitamin D. Again the evidence was radiological and no balance data were given. Steendijk (1961) was able to obtain similar results in a single patient, but again no balance data were given and the possibility of rearrangement of total body calcium rather than an increase in total calcium retention was frankly considered as a possible explanation.

Although phosphate infusions might raise the plasma inorganic phosphate to normal, it is difficult to see how they could lower the faecal calcium, an essential step in the cure of the patient illustrated in Fig. 3. However, Fig. 3 shows that the failure in retention of absorbed calcium was accompanied by a failure of plasma inorganic phosphate to reach normal levels and it is possible that had the plasma inorganic phosphate been raised by phosphate infusions at the same time as vitamin D was administered a very favourable calcium balance might have been established. In order to try and evaluate the use of phosphate therapy, balance studies have therefore been carried out on two further patients with type I (Dent, 1952) renal tubular (hypophos-

phatemic) rickets and osteomalacia respectively. The patient with rickets was on vitamin D therapy throughout in the form of 1.25 mg. vitamin D₂ twice daily. With no other therapy he was in negative calcium balance of 100-150 mg./day with urinary calcium of about 600 mg./day; the plasma inorganic phosphate was 2.0 mg./100 ml. Following intravenous infusions of 'neutral' sodium phosphate of pH 7.4 for six days, the plasma inorganic phosphate rose to 3.5-4.0 mg./100 ml., the faecal calcium was unchanged, but the calcium balance became positive due to a fall in urinary calcium to about 440 mg./day. Following this, increasing doses of the same phosphate mixture were given orally for 18 days during which the plasma phosphate rose steadily to 5.4 mg./100 ml. (plasma calcium remaining normal); the urinary calcium fell to 100 mg./24 hours, but the faecal calcium rose from 450-750 mg./24 hours, thus achieving a positive balance of 100 mg./24 hours. It seemed from this study that a rise in plasma phosphate would lower the urinary calcium, but either this rise itself did not affect faecal calcium if the load was given intravenously, or else raised the faecal calcium if given orally. The patient with the osteomalacia was studied first with no therapy when the faecal calcium was equal to the (normal) dietary intake and the urinary calcium about 90 mg./24 hours. Following intravenous phosphate for five days the plasma phosphate rose from 2.2-4.4 mg./100 ml. and the urinary calcium fell to about 30 mg./24 hours. The faecal calcium was unaffected however so that the intravenous phosphate therapy alone seemed incapable of producing a positive calcium balance. In the next 12 days the plasma inorganic phosphate was maintained at 2.9 mg./100 ml. by giving the phosphate load orally. There was a small rise in faecal calcium which offset the continued lowered urinary calcium. In the next 12 days no phosphate supplement was given, but vitamin D₃ (8 mg./day) was given. This was followed by a fall in plasma inorganic phosphate back to about 2.2 mg./100 ml. and the effect on the calcium balance was as in periods 3 and 4 of Fig. 3, the rise in urinary calcium being slightly greater than the fall in faecal calcium. In the next 12 days oral phosphate therapy and the vitamin D₃ were given together. The plasma inorganic phosphate rose to 4.0 mg./100 ml., the faecal calcium continued to fall, but the urinary calcium now fell to 150-200 mg./24 hours and a positive calcium balance of 400 mg./24 hours was achieved. This treatment was continued as an out-patient and she made a rapid clinical recovery. These results are consistent with the observations both of Frame and Smith

(1958) that oral phosphate therapy increased the positive calcium balance of a boy with vitamin D-resistant rickets who was already on vitamin D therapy, and with those of Frame, Smith, Fleming and Manson (1963) that oral phosphate alone did not improve the calcium balance of a woman with D-resistant osteomalacia. They show that while phosphate therapy alone can lower the urinary calcium, this cannot replace vitamin D which is required to promote absorption of dietary calcium.

Summary

Radiological evidence strongly suggests that osteoporosis (with the possible exception of acute immobilization osteoporosis) may be an irreversible condition. The changes therefore to be expected in calcium balance when an osteoporotic

is treated are small compared with those often seen in osteomalacia. Methods of obtaining more accurate calcium balances are needed to show these small changes, especially when a high calcium intake is used. The method of continuous marking of stools with chromium sesquioxide seems to provide just such a method. Using this method, it has so far proved impossible to obtain prolonged large positive calcium balances in osteoporosis on either high calcium intake, anabolic hormones, or sodium fluoride.

Two alternative therapies to vitamin D have been explored for use in vitamin D-resistant osteomalacia. ATP has been found to be ineffective. Intravenous phosphate alone has been ineffective in producing positive calcium balances, but is effective as a complement to vitamin D under certain conditions.

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