absorption to normal by 24 hours. The administration of parathyroid extract to normal dogs also increased the calcium absorption rate significantly.

Cramer *et al.* (1963) showed that the calcium absorption rate was depressed during periods of hypercalcæmia and that the extent of this fall was greater than that which followed total parathyroidectomy. However, intravenous calcium infusion of parathyroidectomized dogs produced no significant change in the rate of net calcium absorption from the jejunal loop. They concluded that a parathyroid factor, which may be calcitonin, may be responsible for the reduction in calcium absorption rate which occurs during hypercalcæmia in the normal dog.

Copp & Cameron (1961) have demonstrated in dogs that commercially available parathyroid extract appears to exert a short-lived hypocalcæmic effect as well as the well-recognized longer-lived hypercalcæmic action.

In conscious thyro-parathyroidectomized sheep we have shown that the intravenous infusion of commercial parathyroid extract is at first accompanied by slight reductions in both the plasma calcium and magnesium concentrations. Moreover, there is a sharp reduction in the net absorption rate of each of these elements from a Thiry-Vella loop of mid-ileum, followed later by a return to normal levels. Thyro-parathyroidectomy was followed by a reduction in the absorption rate of calcium but not to values as low as those noted during the perfusion of parathyroid extract. This is in accord with the suggestion that the commercial parathyroid extract contains a substance which reduces calcium absorption. This parathyroid extract exerted a similar effect on the absorption rate of magnesium. Preliminary results suggest that thyro-parathyroidectomy decreases the absorption rate of magnesium from the ileum.

The intravenous injection of a calcitonin preparation (kindly supplied by Professor D H Copp) in a sheep with intact parathyroids was associated with a subsequent reduction in the absorption rate of both calcium and magnesium from an ileal loop. There was also a sharp fall in the plasma calcium concentration followed by a compensating rise to a hypercalcæmic level. This rebound effect was not observed in a parathyroidectomized sheep and is presumably the result of natural parathormone release. In the latter case, a significant fall in both plasma calcium and magnesium concentration was observed along with clinical signs of tetany.

We conclude that calcium and magnesium are absorbed in the ileum by a common mechanism and that both parathormone and calcitonin exert effects on this which, although qualitatively similar, are quantitively different.

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The Relation between Calcium Balance and Hydroxyproline Excretion in Osteoporosis

Osteoporosis is a common condition over the age of 50, especially in women. It is associated with a high incidence of back pain and fractures. Albright *et al.* (1941) postulated a relation between osteoporosis and the menopause. They suggested that the loss of gonadal hormones might cause decreased bone matrix formation and so lead to osteoporosis, and this view is still quite widely held. Negative calcium balance would in this case be secondary to the failure in bone formation. Nordin (1960) suggested that osteoporosis might be the result rather than the cause of the negative calcium balance. Whatever the cause, a negative calcium balance must result from either a relative decrease in bone formation rate or increase in bone resorption.

If osteoporosis is the result of a negative calcium balance it should be possible to influence either bone formation or bone resorption by giving calcium supplements and so producing a positive calcium balance. Nordin *et al.* (1964) have shown by isotope techniques that bone resorption is decreased by giving calcium supplements.

Hydroxyproline is an amino acid which is present almost exclusively in collagen. About 40% of the total body collagen is present in the skeleton (Lightfoot & Coolridge 1948). Urinary hydroxyproline excretion is thought to reflect collagen breakdown (Prockop & Sjoerdsma 1961) and it is likely therefore that it would be influenced by bone resorption. High values have been reported in Paget's disease and hyperparathyroidism with bone disease where bone turnover is known to be high, and low values have been reported in hypoparathyroidism (Benoit *et al.* 1963). If calcium supplements decreased bone resorption it would be expected that the urinary hydroxyproline would fall.

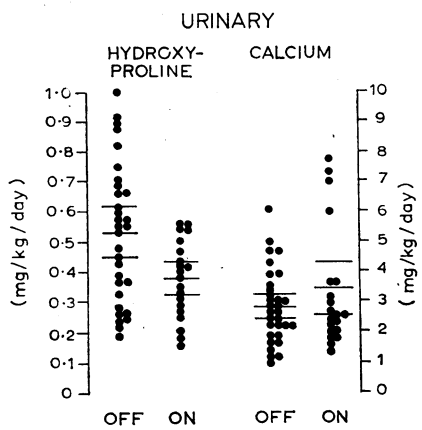

Fig 1 *The urinary hydroxyproline output is shown in 42 osteoporotic patients in the first two columns. On calcium supplements there is a significant fall in the twenty-four-hour urinary hydroxyproline. There was no significant change in the urinary calcium output (last two columns)*

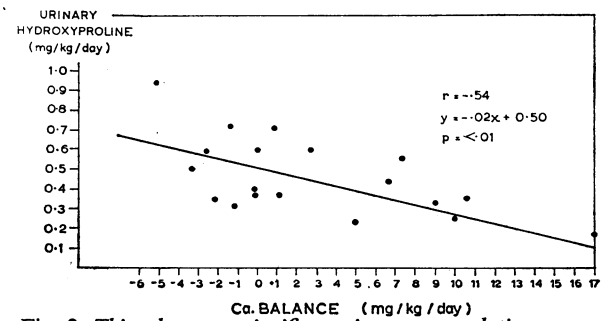

Fig 2 *This shows a significant inverse correlation between calcium balance and urinary hydroxyproline output in 9 osteoporotic and 2 normal subjects*

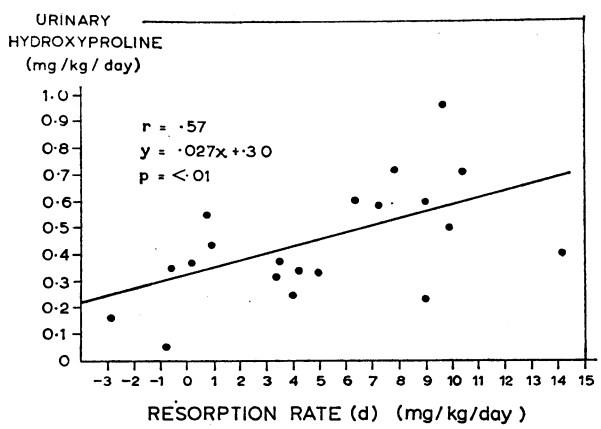

Fig 3 *There is significant direct correlation between bone resorption rate measured isotopically, and urinary hydroxyproline output in 9 osteoporotic and 2 normal subjects*

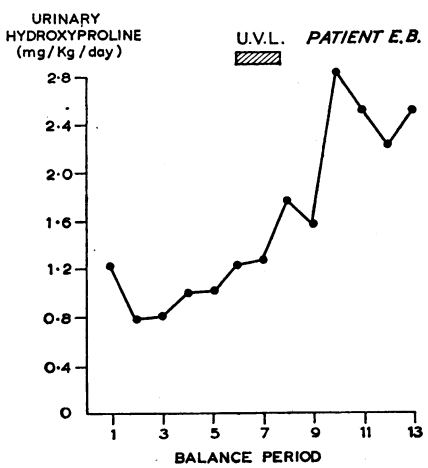

Fig 4 *The urinary hydroxyproline output in a patient with osteomalacia showing the high basal output, and rise following treatment with ultra-violet light*

The study of hydroxyproline output on varying calcium intakes forms the basis of this study.

Methods

Total urinary hydroxyproline was measured by the method of Prockop & Udenfriend (1960). Calcium was measured by a modification of the AutoAnalyzer technique (McFadyen *et al.* 1964). Phosphorus was measured by the standard Technicon AutoAnalyzer technique. Balances were performed over seven-day periods in a metabolic ward. Bone mineralization rates were measured by continuous feeding of isotope (Nordin *et al.* 1964). Bone destruction rates were measured by the difference between bone mineralization rate and calcium balance. The phosphate excretion index (PEI) was calculated as described by Nordin & Fraser (1960).

Results

The twenty-four-hour urinary hydroxyproline output and calcium excretion in 42 osteoporotic patients is shown in Fig 1. The studies were carried out on their normal intake and then at least seven days later while on a supplement of calcium glycerophosphate which supplied an extra 1,100 mg of calcium per day. Nine of the patients were studied on both high and normal intakes, and the remaining 33 patients on either high or normal intake.

We have found the normal hydroxyproline output in this age group to range from about 0·2 to 0·5 mg/kg/day. The mean hydroxyproline output in the osteoporotic patient is 0·53 mg/kg/day, and the range extends well beyond the normal (Fig 1). On the calcium supplements, the mean output is 0·38 mg/kg/day. The difference is significant ($P<0·01$). The mean twenty-four-hour urinary calcium rose from 2·8 to 3·4 mg/kg/day, but this change was not significant (Fig 1).

Nine patients with osteoporosis and 2 without any disorder of calcium metabolism were studied while on balance. The results are shown in Fig 2. The urinary hydroxyproline excretion was measured over seven-day periods. There is a significant negative correlation between the urinary hydroxyproline output and the calcium balance ($P<0·01$) (that is, the greater the positive balance the lower is the hydroxyproline output). Fig 3 shows the relation between the hydroxyproline output and the bone resorption rate. Here there is a significant positive correlation between the two ($P<0·01$): the higher the bone resorption rate, the higher is the urinary hydroxyproline output.

A low serum calcium and phosphate and raised PEI are typical of osteomalacia. Studies on one patient in negative calcium balance showed that following the administration of ultra-violet light for twelve days there was a rapid rise in the plasma levels of calcium and phosphorus to normal, and the PEI fell to within the normal range. The patient, however, remained in negative calcium balance. The rise in serum calcium must, therefore, have been due to increased bone resorption. If the patient were to remain in negative balance it would be expected that with the healing of the osteomalacia she would develop osteoporosis. The bone resorption rate, measured by continuous feeding of isotope, was 18 mg/kg/day. Following treatment with ultra-violet light it rose to 40 mg/kg/day.

Fig 4 shows the urinary hydroxyproline output in this patient over the same period. The hydroxyproline output was high initially, but following the administration of ultra-violet light there was a sustained rise to double the control values. At this point the patient was given an infusion of calcium gluconate (22·5 mg/kg) over six hours. Following this there was a substantial fall in the urinary hydroxyproline output from 2 to 1·1 mg/kg/day in the twenty-four hours during and after the calcium infusion.

Summary and Conclusions

We believe that urinary hydroxyproline excretion reflects bone resorption rather than new bone formation as suggested by Klein *et al.* (1962). Certainly high urinary hydroxyproline excretion occurs in those conditions where the bone formation rate is high, but the bone resorption rate is also raised in these conditions. We have found that the bone resorption rate when measured by the continuous feeding of isotope is lowered by giving calcium supplements (Nordin *et al.* 1964).

In the present study the urinary hydroxyproline in osteoporotic patients fell with the administration of calcium supplements. The hydroxyproline output was greatest in patients in negative calcium balance and lowest in patients in strongly positive balance achieved by calcium supplements. The urinary hydroxyproline is directly related to the bone resorption rate measured isotopically. The urinary hydroxyproline output in a patient with osteomalacia treated with ultra-violet light was shown to fall with a calcium infusion.

It is concluded that the administration of calcium supplements to patients with osteoporosis leads to a positive calcium balance by causing a decrease in bone resorption.

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Meeting May 27 1964

The following cases were shown:

Functioning Adrenal Graft
Dr J G G Ledingham (for Dr R I S Bayliss)

Bilateral Virilizing Adrenal Tumours
Dr S Leonard Simpson

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Macromastia and Diabetes
Dr P J Watt (for Dr I C Gilliland)

Intersex – Gonadal Dysgenesis with Unilateral Abdominal Testis
Dr K E W Melvin (for Professor Russell Fraser and Dr D J Harrison)

Giant Cell Granuloma of the Pituitary
Dr M Faulkner (for Dr David Ferriman)