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THE EFFECTS OF CALCITONIN
ON THE METABOLIC DISTURBANCES SURROUNDING
WIDESPREAD BONY METASTASES

By
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ABSTRACT

Seven patients with widespread bony metastases, with and without hypercalcaemia were given porcine or salmon calcitonin in an attempt to reduce that rate of progression of their disease, possibly to reduce pain and to accelerate healing during the course of other endocrine therapy. The latter included the administration of phosphate, steroids, androgens or oestrogens and hypophysectomy. Calcitonin effects were seen to be enhanced by simultaneous administration of phosphate and possibly antagonised by oestrogens. The metabolic changes that did occur suggested that the rate of healing of metastatic bone disease was increased and the mechanisms of these changes are discussed.

Metastatic malignant cells in bone may induce changes there in a variety of ways:

(a) By direct invasion of the bone marrow with lysis of bone elements by the combined effects of osteolysis, "pressure", ischaemia or hyperaemia (Shivas et al. 1963; Gorenham & Test 1964). The effects are similar to those of fracture-pain, oedema and deformity and at the microscopic level, a mixture of inflammatory and reparatory changes (Galasko 1972).
(b) By the hormonal stimulation of the normal bone cells to increase the rate of bone destruction. The clinical presentation is one of bone pain, although fracture may be a late presenting feature. Histologically, the picture is similar to that of hyperparathyroidism: an increase in osteoclastic activity, multiple resorption cavities not lined by malignant cells and an excess of woven bone (Galasko 1972). Increased levels of immunocreative parathyroid hormone have been found in patients in this group (Tashjian et al. 1964; Sherwood et al. 1967). Studies of the urinary excretion of calcium in patients with carcinoma of the breast when compared with the plasma calcium concentration, suggested increased tubular resorption of calcium, a finding typical of hyperparathyroidism (Nordin & Peacock 1969). Studies with \(^{47}\text{Ca}\) in these patients suggested an overall increase in bone turnover in keeping with a diffuse hormonal change (Parsons et al. 1970).

(c) A third possible mechanism is inhibition of the action of Vitamin D by the tumour, by production of a local deficiency of phosphate giving rise on a minor scale to what is sometimes mistaken for Vitamin D resistant rickets. This mechanism may explain the predominant osteoid seams seen close to some bone marrow deposits (Follis 1950).

(d) A rare mechanism postulated by Gordon et al. (1967), is the production by some breast carcinomas of an osteolytic sterol, resulting in the developments of bone lysis without the presence of metastases – Stephen Paget's disease of bone (Gordan et al. 1971).

On the basis of all these mechanisms it would seem likely that calcitonin can interfere with some of the lytic processes whether or not there is hypercalcaemia. Bijvoet et al. (1968) previously considered the indication for calcitonin therapy in the majority of treated patients (Foster et al. 1966a,b; Milhaud & Job 1966; Pak & Wills 1968; Foster 1968; Kammerman & Caufield 1970). The simultaneous administration of phosphate salts steroid hormones and other therapy was to some extent unavoidable, since several patients were admitted to the trial with their therapy already of proven benefit. The treatment regime was simplified by stopping radiotherapy and most other therapy for some time before commencing calcitonin therapy. It was not expected that calcitonin would be inhibited by any of the therapies in use, although phosphate administration had been shown to enhance the action of calcitonin in mammals (Hirsh 1968).

METHODS

Patients were referred for trial who already had histological, together with radiological or isotope scan, evidence of secondary deposits in bone. All these patients had undergone courses of conventional endocrine or radiotherapy. Patients were admitted
to the ward for base-line measurements and placed on relatively low (600 mg) calcium intake, since many were receiving such quantities of analgesics that their appetite and food intake were particularly limited. Calcitonin, either porcine or, in the last patient (MC), salmon, was given in 6-hourly, 40 MRC units per dose. Serum and urine chemistry were monitored by methods in use in this hospital group (Anderson et al. 1967). Scans were carried out using $^{85}$Sr or $^{87}$Sr (Parsons et al. 1968).

**CASE HISTORIES**

**Case 1**

JB, a 55 year old civil servant suffered from rheumatoid arthritis for eleven years and from chronic bronchitis for several years. He had had courses of steroids which were thought to be the cause of the sudden onset of severe back pain with neurological signs suggesting cord compression at the level of D9. Investigations revealed a Hb of 10.2 g/100 ml, a W. B. C. of 6800/mm$^3$ and an E. S. R. of 80 mm/h, a blood urea of 26 mg/100 ml and a urinary calcium ranging from 129 to 174 mg/24 h. A chest X-ray showed signs of collapse at the base of the right lung and myelography showed a small extramedullary mass beside the left penduncle of L2. A biopsy of this area (Mr. J. McCabe) revealed a mucin-secreting adenocarcinoma. DXT was instituted for a month with very little amelioration of the pain. This was followed by a course of calcitonin with some relief of his pain. A month later, the patient developed bronchopneumonia and died. At post mortem, an infiltrating carcinoma of the R. L. lobe bronchus was found invading blood vessels, the lung, parenchyma and the pleura. Bone of the lumbar vertebrae showed deposits of the same tumour with moderate osteoblastic response.

**Case 2**

MO, a 70 year old widow presented with symptoms of back pain. Eight years previously she had undergone a right radical mastectomy for adenocarcinoma of the right breast.

Investigations revealed a Hb of 12.8 g/100 ml, W. B. C. of 7700 mm$^3$ and an E. S. R. of 52 mm/h. Radiological examinations showed the presence of multiple metastases in the right ribs and thoracic vertebrae confirmed by an increased uptake on $^{85}$Sr scans. She was treated with calcitonin with some subjective relief and during therapy the turnover of $^{85}$Sr in the vertebrae was slower than after therapy had discontinued (Fig. 8). Her symptomatic improvement was maintained, analgesics were lessened until she developed signs of cord compression at D8 level whereupon she progressed rapidly dying with hypertension not long after. Post mortem showed metastases in the right lung, and anaplastic carcinoma in the D8 vertebrae and left ventricular hypertrophy.

**Case 3**

EH, a 50 year old married woman presented with severe back pain in 1968, and was noticed to have an inoperable carcinoma of the breast on the left with evidence of spread beyond the breast. Investigations revealed a Hb of 10.6 g/100 ml, W. B. C. of 4500/mm$^3$ and an E. S. R. of 45 mm/h, Na of 132 mEq./l, K$^+$ 4.0 mEq./l and urea of 48 mg/100 ml. Urine Ca ranging from 174 to 89 mg/24 h.
Radiological examination revealed widespread bony metastases throughout the spine and ribs. Calcitonin was given with minor subjective changes over a period of one month, but her pain was such that hypophysectomy was carried out and she lived a further eight months before dying at home.

Case 4

FR, a 52 year old married woman, a known diabetic for 9 years, presented with a three week history of joint pains in the upper arms and spine. Investigations revealed a Hb of 14.4 g/100 ml, W. B. C. of 7200 mm$^3$ and an E. S. R. ranging from 38–63 mm/h, Na of 130 mEq/l, K$^+$ of 3.5 mEq/l, HCO$_3$ of 25 mEq/l and urea of 39 mg/100 ml, and a urine calcium ranging from 145 to 38 mg/24 h.

Radiological examination showed osteolytic deposits in the shoulder girdles on both sides, extensive deposits in the lumbar spine and both femora. Chest radiography, barium meal studies and an intravenous pyelogram did not reveal the site of the primary. Her primary treatment was radiotherapy to the osteolytic areas with some amelioration of her pain, she continued to have symptoms. Calcitonin was given with some effect in the control of her pain and her diabetes required almost double the dose of insulin to control her blood sugar while on calcitonin treatment. Her condition continued to deteriorate with the development of a leuco-crythroblastic peripheral blood picture.

Post mortem revealed multiple metastases in many bones possibly stemming from a small primary in the pancreas.

Case 5

MC, a single 50 year old woman was employed as a laundry packer. Presented four years previously with a mass in the right breast and radiological evidence of altered bone structure in the pelvis and upper left femur. A radical mastectomy and bilateral oophorectomy was carried out and testosterone therapy was given over a period of months.

She was able to return to work only to return two years later with persistent lumbar pain and radiological examinations showed considerable increase in the bone changes in the pelvis and lumbar spine. She received a course of DXT to the lumbar spine.

Two months later she developed pain in the back and a lumbar root lesion. A Y90 implant was introduced into the pituitary in 1968 with immediate effects on the root pain. She was maintained on thyroxin and steroids after this.

Within five months, her skeletal pain had re-occurred. Further radiotherapy was given together with oestrogens and then androgens (Durabolin$^\circledR$). She was admitted for review two years after the Y90 implant. Investigations at that time revealed a Hb of 11.9 g/100 ml, a W. B. C. of 8000/mm$^3$ and an E. S. R. of 114 mm/h. Estimation of her electrolytes showed an Na$^+$ of 140 mEq/l, K$^+$ of 3.7 mEq/l, HCO$_3$ of 28 mEq/l and a urea of 26 mg/100 ml. Urine calcium excretions varied from 388 to 814 mg/24 h. Calcitonin was given in two courses (see Fig. 5) with little improvement. Cyclophosphamide was given for a period following this. She was discharged only to be re-admitted with a fractured hip. Further course of DXT were given. Vitamin D was added to the treatment regime followed by a further course of calcitonin without much effect on the moderate hypercalcaemia. Stilboestrol was again given in the place of Durabolin with striking effect on the hypercalcaemia and easing of her bone pain.
Table 1.
Summary of patients' status, type of malignant disease, evidence of bone metastases and treatment used in each patient.

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Malignant disease</th>
<th>Scan and radiological signs of secondaries</th>
<th>Previous treatment not sustained during calcitonin treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>JB</td>
<td>M</td>
<td>55</td>
<td>Carcinoma, bronchus</td>
<td>Lumbar spine</td>
<td>DXT testosterone</td>
</tr>
<tr>
<td>2.</td>
<td>MO</td>
<td>F</td>
<td>70</td>
<td>Carcinoma, breast</td>
<td>Thoracic spine and ribs</td>
<td>Radical mastectomy</td>
</tr>
<tr>
<td>3.</td>
<td>EH</td>
<td>F</td>
<td>50</td>
<td>Carcinoma, breast</td>
<td>Spine</td>
<td>Hypophysectomy</td>
</tr>
<tr>
<td>4.</td>
<td>FR</td>
<td>F</td>
<td>56</td>
<td>Carcinoma, primary probably pancreas</td>
<td>Shoulder girdle and both femora</td>
<td>DXT</td>
</tr>
<tr>
<td>5.</td>
<td>MC</td>
<td>F</td>
<td>50</td>
<td>Carcinoma, breast</td>
<td>Widespread through spine and pelvis</td>
<td>Mastectomy/oophorectomy and hypophysectomy</td>
</tr>
<tr>
<td>6.</td>
<td>KR</td>
<td>F</td>
<td>45</td>
<td>Carcinoma, breast</td>
<td>Scapulae and pelvis</td>
<td>Radical mastectomy and oophorectomy</td>
</tr>
<tr>
<td>7.</td>
<td>SC</td>
<td>F</td>
<td>45</td>
<td>Carcinoma, breast</td>
<td>R. pelvic girdle</td>
<td>Radical mastectomy and steroids</td>
</tr>
</tbody>
</table>
Table 2.

Plasma and serum concentrations of calcium phosphate, total urinary hydroxyproline (THP) and serum alkaline phosphatase (SAP) before treatment with calcitonin and during treatment (+ supplements).

<table>
<thead>
<tr>
<th></th>
<th>Mean of values before</th>
<th>Lowest value during therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ca++ mg/100 ml</td>
<td>PO₄⁻ mg/100 ml</td>
</tr>
<tr>
<td>JB</td>
<td>8.9</td>
<td>3.08</td>
</tr>
<tr>
<td>MO</td>
<td>8.1</td>
<td>3.4</td>
</tr>
<tr>
<td>EH</td>
<td>8.9</td>
<td>3.7</td>
</tr>
<tr>
<td>FR</td>
<td>10.6</td>
<td>3.2</td>
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<tr>
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<td>2.8</td>
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<tr>
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<td>14.0</td>
<td>4.5</td>
</tr>
<tr>
<td>SC</td>
<td>9.3</td>
<td>3.4</td>
</tr>
</tbody>
</table>
Fig. 1.
Plasma calcium and phosphate concentrations with total urinary hydroxyproline excretion before treatment with oral phosphate (slow P) and then with calcitonin in patient JB.

Fig. 2.
Serum calcium, plasma phosphate, total urinary hydroxyproline and urinary calcium excretion during treatment with calcitonin (CT 160 U/24 h) black bars, and phosphate supplements (5.4 g PO₄ daily) open bars, in patient MO.
Fig. 3.
Serum calcium, plasma phosphate, total urinary hydroxyproline and urinary calcium excretion during treatment with calcitonin (CT 160 U/24 h) oral phosphate (2.4 g/24 h) and Vitamin D (40 000 IU/24 h). An arrow ↓ marks the operation of hypophysectomy in patient EH.

Fig. 4.
Plasma calcium phosphate, alkaline phosphatase and total urinary hydroxyproline and calcium excretion during treatment with calcitonin, black bars and oral phosphate, open bars in patient FR.
Plasma calcium, total urinary hydroxyproline, serum uric acid and plasma phosphate and alkaline phosphatase during treatment with steroids (cortisone 75 mg/24 h), Durabolin (25 mg/24 h) following a 90Y implant of the pituitary thyroxine supplements (1.0 mg twice daily). Phosphate was given in dose of 4.4 g elemental phosphate daily (hatched bars) and calcitonin 160 U daily (black bars). Sodium fluoride was added (40 mg NaF daily) and Vitamin D (20 000 IU/24 h) and finally stilboestrol (20 mg/24 h) and finally ZnSO₄ (200 mg t. d. s.) ↓ in patient MC.
Plasma calcium, total urinary hydroxproline, plasma alkaline phosphatase, serum phosphate and uric acid during treatment with stilboestrol (20 mg/24 h) open bar, phosphate supplements (4.4 g slow P daily) hatched bar and calcitonin (160 U/24 h) (black bar) in patient SC.

\[\text{Fig. 7.}\]

\[^{85}\text{Sr} \text{ counts (corrected for decay) over several areas of metastatic infiltrations and relatively normal bone during treatment with calcitonin 160 MRC units daily (black bars).}\]

\[\text{After cessation of treatment turnover of the deposited isotope seems to increase.}\]

\[\text{Fig. 6.}\]

Serum calcium, total urinary hydroxyproline, plasma uric acid, phosphate and alkaline phosphatase during treatment with Durabolin (25 mg/24 h) open bars, steroids (cortisone 75 mg/24 h) open bar, oral phosphate (3.6 g slow P daily) hatched bar, calcitonin (160 U/24 h) black bar and interchanging (1.4 mg/24 h) open bar in patient KR.
She was mobilised to be discharged home again, but died there of pneumonia some four months later.

Case 6

KR, a 44 year old housewife had had a radical mastectomy for an adenocarcinoma of the breast four years previously with no evidence of spread beyond the breast. She had received a course of radiotherapy immediately following the operation. Two years later she had pain in the hip and a 75Sr scan suggested metastases which were irradiated in the following year. The pain recurred and four years after the first operation, a bilateral oophorectomy was carried out followed by further radiotherapy to the pelvis and ribs. After this Durabolin was given and in the following month her serum calcium had risen. Other investigations revealed a Hb of 11.6 g/100 ml, a W. B. C. of 6700/mm3, a Na 139 mEq./l, K+ of 2.6 mEq./l and a blood urea of 62 mg/100 ml urine calcium of 256 mg/24 h. The Durabolin was stopped, phosphate salts given with little response. A hypophysectomy was carried out and supplements of cortisone, thyroxine and pitressin were given. The hypercalcaemia persisted and calcitonin was given over a three week period with an immediate lowering of the hypercalcaemia. Her pain eased, she was mobilised and she was allowed home only to be re-admitted two months later with a calcium of 22.4 mg/100 ml which responded slightly to further administration of calcitonin and Mithramycin®, but not before irreversible renal damage had occurred and the patient died of uraemia a week later.

Case 7

SC, a 44 year old married housewife presented four years previously with a lump in the breast and a radical mastectomy was carried out for a poorly differentiated adenocarcinoma which had involved at least two axillary lymph nodes. She refused oophorectomy and had a course of radiotherapy to the chest. She was admitted in 1970 with pain in the right hip and had a further course of radiotherapy to the pelvis and hip region and then she was started on the androgen, Durabolin. Investigations revealed a Hb of 14.9 g/100 ml, a W. B. C. of 6000/mm3 and an E. S. R. of 14 mm/h, Na of 139 mEq./l and a urea of 15 mg/100 ml. Her urine contained 252–298 mg Ca/24 h and her creatinine clearance was 51 ml/min. Radiological survey showed secondary deposits in the ribs, lumbar spine, pelvis and right femur throughout its length with a pathological fracture in the mid shaft. stilboestrol was substituted for Durabolin and an oral phosphate mixture was given with little effect on her pain or other symptoms. Calcitonin was given and the stilboestrol stopped and slow release phosphate continued. Her pain eased. There was evidence of new periosteal bone formation near the pathological fracture and she was mobilised and allowed home in a wheel chair only to be re-admitted a month later with mediastinal and oesophageal obstruction from which she died.

RESULTS

The seven patients treated are shown in Table 1, together with their radiological and scan findings. Pre-treatment biochemistry is shown in Table 2. Figs. 1–7 show changes in biochemistry during treatment for each patient. Fig. 8 shows the sequential changes in the scan counts during and after therapy.
Changes in serum calcium during treatment

Patients EH, MO, JB, FR and SC were normocalcaemic during treatment with calcitonin. Patients KR and MC were hypercalcaemic (serum calcium 10.8 mg/100 ml) when treatment was commenced. Very slight falls (0.5 to 0.7 mg/100 ml) were recorded in FR and EH; MO and JB did not change significantly until phosphate salts were administered and SC showed no change even with the addition of phosphate.

The two hypercalcaemic patients showed striking falls from 12.5 mg/100 ml to 9.8 ml/100 ml (MC) and from 15.1 to 9.5 mg/100 ml (KR). Phosphate administration enhanced falls in normocalcaemic patients MO, FR and EH, while JB experienced tetany with a serum calcium of 6.8 mg/100 ml.

Phosphate therapy alone did not affect the serum calcium significantly when commenced before calcitonin therapy in JB or after therapy in MO: a change to a lower dosage in FR led to a slight rebound, but calcitonin administered with the reduced phosphate dosage continued to exert a hypocalcaemic effect. In EH there were variable effects due to simultaneous administration of Vitamin D.

It is to be noted that the cessation of calcitonin therapy in those patients receiving phosphate supplements led to a rise in serum calcium in patients MO (two occasions), JB (one occasion), EH (two occasions), MC (two occasions); the hypocalcaemic effect persisted in KR, and was probably related to the effect of a previous hypophysectomy – the hypocalcaemia was, however, short-lived, the serum calcium returning to 22.3 mg/100 ml within two months.

SC provided the interesting observation that until her stilboestrol therapy was discontinued, the calcitonin therapy whether alone, or supplemented by phosphate had no effect on serum calcium: a sustained but slight fall in serum calcium occurred as soon as the hormone was withdrawn. Changes in urinary calcium output paralleled serum calcium concentrations: this is shown particularly well in the case of MO.

Changes in serum phosphate during treatment

Slight falls in serum phosphate were observed in patients MO, JB and KR, when treated with calcitonin alone; JN did not show significant falls until phosphate supplements were added, suggesting that bone healing was taking place. In patients EH, FR, MC and SC, changes were minimal and observed only by transient rises due to phosphate administration.

Changes in serum alkaline phosphatase

All the normocalcaemic patients showed little or no change in alkaline phosphatase during calcitonin therapy, while of the two hypercalcaemic patients MC showed no change with calcitonin but large increases with Vitamin D.
and KR showed large increases when calcitonin was administered accompanying the fall in serum calcium.

Changes in total urinary hydroxyproline (THP) output

JB, the first patient to be treated in this series, did not have this estimation carried out at sufficiently frequent intervals for the results to be interpreted reliably, but there was a tendency for the output to increase slightly on treatment only to settle to normal values during the hypocalcaemic episode.

FR showed a striking rise only after calcitonin treatment had ended, phosphate therapy being continued: a fall occurred after a time and total urinary hydroxyproline (THP) did not rise again during the second period of calcitonin administration. Similar slight but fluctuant increases were recorded in MO and EH, in the latter case particularly after the administration of Vitamin D. Sustained falls were seen in one hypercalcaemic patient MC, but the opposite occurred in the other, KR: THP rising to even higher values after the cessation of therapy. A similar rise was seen in MC when Vitamin D was given, coinciding with the rise in alkaline phosphatase, both measurements settling later to normal, coinciding with a fall in serum calcium, on stilboestrol therapy.

Fig. 9.
Radiographs of a fractured femur in SC showing a new periosteal bone formation after treatment with calcitonin.
Subjective changes

JB and FR noticed slight amelioration in their metastatic pain, which had so far been progressive despite courses of radiotherapy. MO became pain free, and post-therapy nursing, despite her age, was made much easier.

Pain progressed despite therapy in EH, who later underwent hypophysectomy with some relief of symptoms. The two hypercalcaemic patients noticed immediate improvement in their pain and conditions coincident with the lowering of serum calcium, and KR was discharged from hospital able to move about for the first time in several months. Unfortunately she was re-admitted too late for a second course of calcitonin, this time combined with Mithramycin to have much effect. SC was able to leave hospital with considerable relief of her pain, despite widespread secondary deposits and a femur fractured in several places which had formed a callus (Fig. 9). She was re-admitted later with oesophageal obstruction and died rapidly without recrudescence of her bone pain.

It is noticeable that patients experiencing most relief were those with carcinoma of the breast; but the series is a small one.

DISCUSSION

The reason for using calcitonin in this group of patients with bone pain from secondary deposits, was that other therapies, such as endocrine and radiotherapy had ceased to control their symptoms effectively, and the pain was accompanied by weakness reminiscent of the symptoms suffered by patients with osteopathies of the type seen in hyperparathyroidism (Bischoff & Esslen 1965) and osteomalacia (Smith & Stern 1967).

If it is conceded that some osteolytic deposits achieve their effect by humoral means, inducing changes in the bone not entirely due to simple erosion, then alternative endocrine therapy might still be effective in helping other symptoms. These studies show that calcitonin in moderate doses induces biochemical changes in the majority of patients suggesting that bone cell resorptive activity was slowed down, shown by falls in serum calcium, accompanied by falls in urinary calcium in keeping with the known action of calcitonin in normal bone cells both in vitro and in vivo, overriding the resorptive activity of parathyroid hormone (Aliapoulios et al. 1966; Anast et al. 1967; O'Riordan & Aurbach 1968; Bordier et al. 1969).

The rises and falls in total urinary hydroxyproline are more difficult to interpret as some of the excreted peptides are the result of the synthesis as well as the destruction of collagen as seen in studies of Paget's disease using labelled proline (Krane et al. 1970) or in the healing of rat rickets (Parsons et al. 1973). On this basis, a fall in excretion of THP can represent a decrease in bone breakdown and a rise as part of the healing tumour induced osteomalacia.
The hypercalcaemic patients showed changes in the serum alkaline phosphatase, reminiscent of the increases seen in patients who have had parathyroid tumours removed (Smith 1969).

Calcitonin action seemed on several occasions to be enhanced by the simultaneous administration of phosphate, the latter being relatively ineffective on its own save in its known action in hypercalcaemic patients (Goldsmith & Ingbar 1966). This mechanism probably acts at a cellular level at the bone cell surface rather than by simply raising the serum phosphate concentration of Cax P04 product, as in one patient (JB) the phosphate concentration fell during the period of maximum effect and was maintained around 3 mg/100 ml in MC. Nichols (1970) used isolated bone cell preparations to demonstrate that increasing the ambient phosphate concentration, prevented calcium efflux from cells stimulated by parathyroid hormone. Acute rises observed in KR were in part due to renal failure secondary to sustained hypercalcaemia.

Calcitonin administration usually reduces THP in patients with an increased bone turnover such as in Paget's disease. However, not every patient demonstrated a decrease in THP during calcitonin therapy.

Steroids interfere with the action of calcitonin, cortisone inhibits the hypocalcaemic action (Thompson et al. 1968) in cortisone treated adrenalectomised rats, while stilboestrol at the concentration of 1 mg/kg body weight, which is not hypercalcaemic, can effectively block the action of calcitonin in female rabbits (Currie & Black 1972). These findings may have some bearing on the failure of calcitonin to act in MC, who was maintained on steroids, and SC, who did not respond until her stilboestrol dosage was reduced.

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