treatment is limited to those patients who show raised free triiodothyronine or thyroxine concentrations, or both, on presentation or who show a rise in free hormone concentrations to above the normal range after treatment of their intercurrent illness. In more doubtful cases a significant TSH response to TRH will exclude hyperthyroidism. We disagree with the advice of Forfar and Toft[11][12] that in elderly patients with atrial fibrillation and normal thyroid hormone concentrations the absence of a TSH response to TRH is grounds for treatment (often destructive) of hyperthyroidism.

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Mechanisms of malignant hypercalcaemia in carcinoma of the breast

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Abstract

To investigate the mechanisms of hypercalcaemia in carcinoma of the breast, 22 patients with hypercalcaemia due to metastatic carcinoma were studied and the findings compared with those obtained in normal subjects and patients with benign and malignant breast disease without hypercalcaemia. As expected, patients with metastases of bone showed biochemical evidence of increased bone resorption. Whereas all patients with hypercalcaemia had skeletal metastases, not all patients with skeletal metastases had hypercalcaemia despite considerable degrees of bone resorption. The presence of hypercalcaemia was associated with a significant increase in renal tubular reabsorption of calcium (p <0·001) and decreased reabsorption of phosphate (p <0·001) despite adequate rehydration of patients.

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These studies suggest that increased renal tubular reabsorption of calcium, possibly mediated by a humoral factor with activity similar to that of parathyroid hormone, contributes appreciably to the hypercalcaemia of malignant breast disease.

Introduction

Hypercalcaemia is a common complication of breast cancer, occurring in 10-25% of patients with disseminated disease.[1-3] The main mechanism of hypercalcaemia is increased bone resorption due either to a direct effect of the tumour on bone or to agents liberated by the tumour that activate osteoclasts.[3][4] The discrepancy between the degree of hypercalcaemia and the extent to which the skeleton is affected by metastases suggests that other mechanisms may be important.[5][6] Among the other organ systems that have a role in homoeostasis of calcium, the contribution of intestinal absorption of calcium to hypercalcaemia is likely to be minimal, as patients with hypercalcaemia have reduced intestinal absorption of calcium and low serum concentrations of $1\alpha,25$-dihydroxycholecalciferol.[7][8] Impaired renal function is likely to be important as dehydration increases renal tubular reabsorption of calcium and thus aggravates hypercalcaemia.[9] Moreover, impaired glomerular filtration, a result of both hypercalcaemia and volume depletion, decreases the ability to excrete a challenge of calcium derived from bone.

Patients and methods

We studied 22 patients with malignant hypercalcaemia due to carcinoma of the breast. Six were receiving treatment with tamoxifen (20 mg daily by mouth), and seven showed biochemical evidence of hepatic metastases. None were taking oestrogens. All showed radio-

ogical evidence of metastases of bone. After admission to hospital they were rehydrated with intravenous saline (4-6 litres daily) for at least 48 hours. All patients remained hypercalcaemic (serum calcium concentration >2·6 mmol/l (10·4 mg/100 ml)) after this initial period and showed no further fall in sequential measurements of calcium, creatinine, albumin, and packed cell volume over 24 hours.

This group was compared with 30 normocalcaemic patients with breast cancer with (n = 17) or without (n = 13) metastases of bone, as judged by radiographs of the skeleton and scintigraphy, 15 patients with benign breast disease, and 10 normal female volunteers.

After an overnight fast the subjects voided their bladders and were allowed to drink distilled water. Urine was collected in acid over the subsequent two hours. Samples of venous blood were obtained midway through the collection of urine. A Technicon SMAC autoanalyser was used to measure serum concentrations of calcium, phosphate, and creatinine and to assess liver function (by measurement of albumin concentrations and activities of alkaline phosphatase and other enzymes derived from the liver). The serum calcium concentration was adjusted to an albumin concentration of 42 g/l (normal range 2·1-2·6 mmol/l (8·4-10·4 mg/100 ml)). In patients with carcinoma of the breast serum concentrations of immunoreactive parathyroid hormone were measured by radioimmunoassay using an antiserum crossreacting predominantly with the midmolecule (amino acid residues 44-68) region of parathyroid hormone.[10] Urinary excretion of calcium, phosphorus, creatinine, and hydroxyproline bound to peptides was measured.[11] Urinary hydroxyproline was expressed as the ratio of urinary hydroxyproline to urinary creatinine concentrations and urinary calcium as the ratio of calcium to creatinine concentrations or the calcium excretion per unit of glomerular filtrate.[12 13] Renal tubular reabsorption of phosphate was expressed as the ratio of maximal tubular reabsorption of phosphate to glomerular filtration rate.[14]
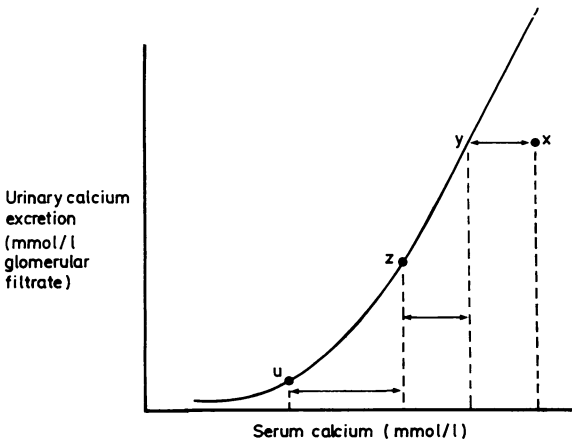

FIG 1—Diagram to illustrate methods of analysing hypercalcaemia. Deviations from the curvilinear relation between serum calcium concentrations and excretion of calcium found in normal subjects are attributable to changes in renal tubular reabsorption of calcium.[13] The increment in serum calcium concentrations due to renal tubular reabsorption = x-y mmol/l. In patients with impaired renal glomerular function excretion of calcium is recomputed using the mean plasma creatinine concentration in the controls (76 μmol/l; 860 μg/100 ml). The increment in plasma calcium concentrations due to abnormal renal glomerular filtration was computed as y-z mmol/l. Any residual increment in serum calcium concentrations compared with control subjects was attributed to increased bone resorption (z-u mmol/l).

The ratio of calcium to creatinine in urine obtained during fasting provides an index of net release of calcium from bone, whereas the excretion of hydroxyproline is an index of bone resorption.[15-17] Components of hypercalcaemia (impaired renal function, increased bone resorption, and increased renal tubular reabsorption of calcium) were assessed from the normal (curvilinear) relation between fasting serum calcium concentration and excretion of calcium after rehydration in the patients with hypercalcaemia.[13 15] Figure 1 summarises this method.

The significance of changes in mean values was assessed using one way analysis of variance and Student's t test for paired or non-paired observations as appropriate. Confidence limits are given as the SEM.

Results

Rehydration of the patients with hypercalcaemia with physiological saline induced a significant fall in serum calcium concentrations (from 3·45 (0·14) mmol/l to 3·17 (0·08) mmol/l (13·8 (0·6) to 12·7 (0·3) mg/100 ml); p < 0·01) associated with a fall in serum creatinine concentrations (136 (18) to 101 (9) μmol/l (1·5 (0·2) to 1·1 (0·1) mg/100 ml); p > 0·1) and in serum albumin concentrations (36·7 (1·2) to 31·7 (1·58) g/l; p < 0·005). Serum concentrations of calcium, albumin, and creatinine were stable and did not decrease further over the subsequent 72 hours, suggesting that rehydration was adequate.

After the initial period of rehydration the biochemical data for the group with hypercalcaemia were compared with those from the healthy subjects, patients with benign breast disease, and patients with normal calcium concentrations with carcinoma with and without skeletal metastases. There were no significant differences in any of the measurements between the healthy subjects and the patients with benign breast disease, and the data for these two groups were pooled (controls).

As expected, patients with hypercalcaemia and skeletal metastases showed considerable biochemical evidence of increased bone resorption as judged by a high urinary excretion of calcium and hydroxyproline (table I). A close correlation was noted between these measurements (r = 0·6; p < 0·01), suggesting that a major source of hydroxyproline was bone rather than tumour tissue. In contrast the high serum activity of alkaline phosphatase correlated with that of γ-glutamyltransferase (r = 0·85; p < 0·02), suggesting that some of the alkaline phosphatase was derived from the liver.

In patients with overt skeletal metastases pronounced and significant differences in urinary excretion of calcium and hydroxyproline were observed between those with and those without hypercalcaemia (table I). Despite these differences there was an overlap in the variables of resorption between those with and those without hypercalcaemia (figs 2 and 3). Thus six of the 17 patients with normal calcium concentrations (35%) had increased fasting calciuria and 10 (58%) had abnormal hydroxyprolinuria. The converse, however, was infrequently observed: only one patient with hypercalcaemia had values for hydroxyproline within the normal reference range. As mean serum concentrations of creatinine did not differ (table I) the difference in serum concentrations of calcium could not be accounted for by differences in renal glomerular function. The high rates of excretion of calcium in some of the patients with normal calcium concentrations suggested that differences in bone resorption could not be the sole factor accounting for hypercalcaemia.

Analysis of the components of hypercalcaemia (table II) showed that, in the patients with hypercalcaemia, only 46% of the increment in calcium concentrations was attributable to net release of calcium from bone and that a similar and significant fraction (40%) was due to increased renal tubular reabsorption of calcium, the remainder

TABLE I—*Mean biochemical variables (SEM) in patients with skeletal metastases due to carcinoma of breast*

	Patients with normocalcaemia	Patients with hypercalcaemia	p	Normal
Serum alkaline phosphatase (IU/l)	213 (66)	230 (26)	NS	35-105
Serum creatinine (μmol/l)	95 (9)	101 (9)	NS	60-120
Serum immunoreactive parathyroid hormone (pmol/l)	135 (18)	85 (18)	<0·05	35-135
Serum phosphate (mmol/l)	1·27 (0·07)	0·85 (0·05)	<0·001	0·6-1·5
Urinary calcium (mmol/mol creatinine)	385 (78)	1730 (235)	<0·001	200-450
Urinary calcium excretion (μmol/l glomerular filtrate)	34 (7)	175 (40)	<0·001	20-40
Urinary hydroxyproline (mmol/mol creatinine)	50·2 (4·7)	86·7 (7·6)	<0·001	10-30
Tubular reabsorption of phosphate: glomerular filtration rate (mmol/l)	1·18 (0·12)	0·54 (0·04)	<0·001	0·9-1·6

Conversion: SI to traditional units—Creatinine: 1 μmol/l ≈ 0·01 mg/100 ml. Phosphate: 1 mmol/l ≈ 3·1 mg/100 ml. Urinary calcium: 1 mmol/mol creatinine ≈ 0·35 mg/g. Urinary calcium excretion: 1 μmol/l glomerular filtrate ≈ 11·6 mg/l. Urinary hydroxyproline: 1 mmol/mol creatinine ≈ 1·16 mg/g. Tubular reabsorption of phosphate: glomerular filtration rate: 1 mmol/l ≈ 3·1 mg/100 ml.

TABLE II—*Mean (SEM) serum concentrations of calcium and increment attributable to abnormal renal and skeletal metabolism*

			Increment of serum calcium (μmol/l) attributable to:		
Group	No of patients	Serum calcium (mmol/l)	Renal impairment	Increased renal tubular reabsorption	Increased bone resorption
Healthy subjects and patients with benign breast disease	25	2·30 (0·01)	2 (4)	−5 (20)	3 (19)
Patients with carcinoma of breast without metastases	13	2·38 (0·02)	26 (9)*	18 (30)	43 (18)
Patients with carcinoma of breast with skeletal metastases and normocalcaemia	17	2·43 (0·02)	31 (18)	34 (40)	72 (36)
Patients with carcinoma of breast with skeletal metastases and hypercalcaemia	22	3·17 (0·08)	121 (50)*	347 (89)*	407 (56)**

Significance of differences from controls: *p < 0·02, **p < 0·001.
 Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml.
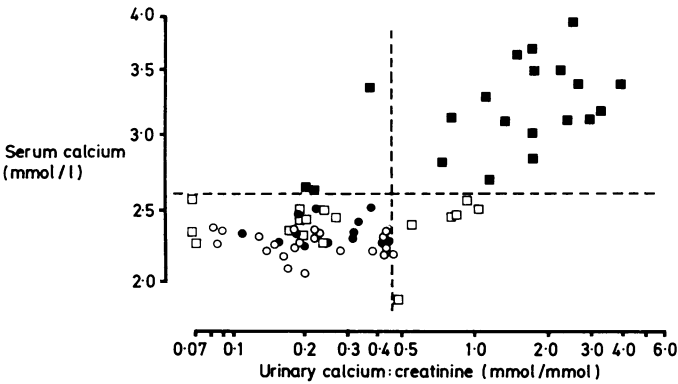

FIG 2—Relation between serum calcium concentrations and ratio of fasting urinary calcium to creatinine excretion in controls (O), patients with carcinoma of breast without metastases (●), patients with skeletal metastases but normocalcaemia (□), and patients with skeletal metastases and hypercalcaemia (■). Dotted lines denote upper limit of normal reference range. Note logarithmic scales.

Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml. Urinary calcium: creatinine: 1 mmol/mol ≈ 0·35 mg/g.
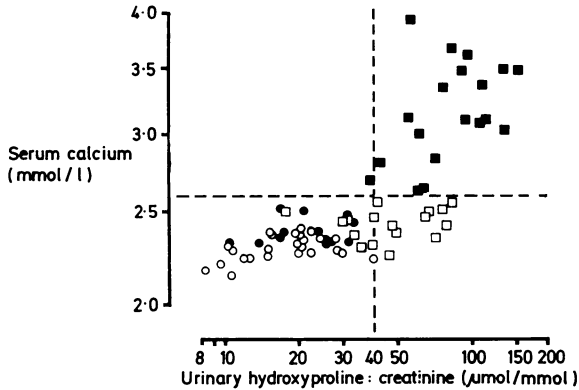

FIG 3—Relation between concentrations and ratio of fasting hydroxyproline to creatinine excretion in controls (O), patients with carcinoma of breast without metastases (●), patients with skeletal metastases but normocalcaemia (□), and patients with skeletal metastases and hypercalcaemia (■). Dotted lines denote upper limit of normal reference range. Note logarithmic scales.

being accounted for by impaired renal glomerular function. The increase in serum calcium concentrations due to renal tubular reabsorption was significantly greater in the patients with hypercalcaemia (p < 0·02) than in the patients with normal calcium concentrations and the controls. All but two patients showed increases in renal tubular reabsorption above normal values, and in nine (41%) this was the major factor maintaining hypercalcaemia.

Increased renal tubular reabsorption of calcium in the patients with hypercalcaemia was associated with hypophosphataemia due to a decrease in the estimated ratio of tubular reabsorption of phosphate to glomerular filtration rate (table I), and a significant inverse correlation was noted between the ratio of tubular reabsorption of phosphate to glomerular filtration rate and serum calcium concentrations (r = −0·66; p < 0·005). There was a correlation between phosphate concentrations and both serum creatinine concentrations (r = 0·5;

p < 0·02) and the ratio of tubular reabsorption of phosphate to glomerular filtration rate (r = 0·6; p < 0·07) but none between serum creatinine concentrations and the ratio of tubular reabsorption of phosphate to glomerular filtration rate (r = 0·003). Mean concentrations of immunoreactive parathyroid hormone were significantly lower in the patients with hypercalcaemia than in those with normocalcaemia (table I).

Discussion

Hypercalcaemia in patients with carcinoma of the breast is almost invariably associated with skeletal metastases. The finding of hypercalcaemia without skeletal disease, termed pseudohyperparathyroidism, was thought to be mediated by humoral agents like parathyroid hormone secreted by the tumour tissue.[18-20] With improved techniques for detecting metastases and increased specificity of assays for parathyroid hormone, however, the apparent incidence of this syndrome has decreased.[3][5] This has led to the widely accepted view that the major cause of hypercalcaemia, particularly in patients with carcinoma of the breast, is a focal increase in bone resorption due to activation of osteoclasts by adjacent tumour tissue.[3] Potential candidates for a paracrine effect of tumour cells on bone cells include prostaglandins of the E series,[21][22] transforming growth factors[3] and factors that activate osteoclasts in the case of myeloma and T cell lymphoma.[23]

Several lines of evidence suggest that this local mechanism may be an oversimplification. Limited histological studies in patients with skeletal metastases including a patient with carcinoma of breast indicate that bone resorption mediated by osteoclasts may be increased at sites distant from the tumour.[24] There is also evidence that some tumour cells can elaborate humoral agents that compete for parathyroid hormone or epidermal growth factor at skeletal receptor sites.[25][26] Thus the degree of hypercalcaemia is often greater than expected from the extent of scintigraphic abnormalities and resection of the primary tumour improves the hypercalcaemia, suggesting that many solid tumours may induce bone resorption at sites distant from metastatic tissue.[5][6] Probably, therefore, tumours increase bone resorption by several different mechanisms, and indeed more than one mechanism may operate in the same tumour type.

Our observations in patients with carcinoma of the breast indicate that hypercalcaemia is invariably associated with increased bone resorption. We cannot tell whether this was mediated by local destruction of bone as we did not assess the extent of skeletal metastases. We did, however, show that this was not the sole factor accounting for the hypercalcaemia, as many patients with normal calcium concentrations had florid biochemical evidence of bone destruction. Indeed, less than 50% of the hypercalcaemia observed was due to increased bone resorption, a major component being caused by increased tubular reabsorption of calcium. This suggests that agents derived from the tumour, as well as affecting the skeleton, may also act on the kidney.

The mechanism for increased renal tubular reabsorption of calcium is not clear. It is well established that severe hypercalcaemia augments renal tubular reabsorption of calcium by a complex series of events, including impairment of concentrating ability, depletion of sodium, and decrements in glomerular

filtration.[9][27] For these reasons we were careful to ensure that patients were volume replete. Nevertheless, the interpretation of our findings depends critically on the adequacy of extracellular volume expansion. In our patients mean serum concentrations of creatinine did not differ from those in patients with normal calcium concentrations (table I) and serum concentrations of both creatinine and albumin remained stable for 48 hours after the collection of urine and serum with continued parenteral saline. In studies of the mechanism of hypercalcaemia in myeloma we showed decreased renal tubular reabsorption of calcium in patients studied in an identical manner.[28] These considerations suggest that inadequate volume expansion was not responsible for the increased renal tubular reabsorption of calcium in our patients with carcinoma of the breast. It is notable that our patients also had a low ratio of tubular resorption of phosphate to glomerular filtration rate and hypophosphataemia. Decreased renal tubular reabsorption of phosphate has been noted previously in such patients but may have been due to the concomitant administration of oestrogens or to renal failure.[29][30] None of our patients, however, were taking oestrogens, and we found no relation between the ratio of tubular resorption of phosphate to glomerular filtration rate and serum concentrations of creatinine. We found a significant inverse correlation between the ratio of tubular resorption of phosphate to glomerular filtration rate and serum calcium concentrations, but it is not possible to determine whether this was a direct effect of hypercalcaemia.

These abnormalities in renal phosphate and calcium transport are comparable with those observed in primary hyperparathyroidism. In addition, some, but not all, investigators have observed increased urinary excretion of nephrogenous cyclic adenosine monophosphate in patients with carcinoma of the breast.[31][32] A hypothesis that might explain our observations is the elaboration by tumour cells of a humoral agent with effects similar to those of parathyroid hormone, but in keeping with other studies concentrations of parathyroid hormone were lower in our patients with hypercalcaemia than in others with skeletal metastases.[3][8][33] It is also important to note that the hypercalcaemia of malignancy is associated with low concentrations of 1α,25-dihydroxycholecalciferol and intestinal malabsorption of calcium.[7][8] In this respect it differs from primary hyperparathyroidism, but this might be due to differences in nutritional state or renal glomerular function.[3][34]

Our findings have implications for the treatment of hypercalcaemia. Whereas inhibitors of bone resorption may decrease the component due to increased bone resorption, they would not affect the increment due to tubular reabsorption. We previously noted that diphosphonates are less effective as hypocalcaemic agents in patients with solid tumours than in those with myeloma despite a similar inhibitory effect on bone resorption,[35][36] which supports this view. The availability of competitive inhibitors of parathyroid hormone for clinical use[3][25] might provide an attractive treatment for this component of hypercalcaemia.

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The Lips which are visible to the eye at the first sight, they are framed of the common coverings of the Body, and have pretty store of spongy fat, their use is to keep the internal parts from cold and dust.

The Nymphae or Wings which appear when the Lips are fevered, they are framed of soft and spongy flesh, and the doubling of the skin, placed at the sides of the Neck; they compass the Clitoris, and in form and colour resemble the Comb of a Cock.

The Clitoris is a sinewy and hard Body, full of spongy and black matter within, as the side ligaments of the yard are, in form it represents the yard of a man, and suffers erection and falling as that doth, this is that which causeth lust in women, and gives delight in Copulation, for without this a woman neither desires copulation, or hath pleasure in it, or conceives by it. Some are of opinion, and I could almost afford to side with them, that such kind of Creatures they call Hermaphrodites which they say bear the genitals both of men and women, are nothing else but such women in whom the Clitoris hangs out externally, and so resembles the form of the yard; leave the truth or falsehood of it to be judged by such who have seen them anatomised: however, this is agreeable both to reason and Authority, that the bigger the Clitoris is in women, the more lustful they are.

Nicholas Culpeper (1616-54)
Directory for Midwives, 1671