Which patients are cured of breast cancer?

I S FENTIMAN, J CUZICK, R R MILLIS, J L HAYWARD

Abstract

The clinical and pathological features of 51 patients who survived for more than 20 years after diagnosis of cancer of the breast were compared with those of 176 contemporaries who died within 20 years after diagnosis. Of those who survived, 18 (35%) had had pathologically affected axillary nodes compared with at least 86 (49%) of those who died. Also, 11 (21%) of the survivors had had small tumours compared with 10 (6%) of those who died. Pathological review of tumours in the survivors showed 40 (78%) to have been infiltrating ductal carcinomas, of which 13 (32%) were grade 3 lesions. These differences between the two groups were largely due to the prognostic value of these variables in the first five years after diagnosis. After a patient had survived five years the major prognostic variables were of little value in the prediction of which patients would be cured of breast cancer. Advanced age, which was of little prognostic value in the first five years after diagnosis, was of significant prognostic value in the longer term, partly due to the steep age gradient for mortality from other diseases. Nevertheless, seven of 19 deaths more than 20 years after first treatment were due to breast cancer. Late deaths from breast cancer may, however, have often been the result of metastases from second primaries rather than the late manifestation of micrometastases from the original primary carcinoma.

Age, menstrual state, clinical stage, and axillary nodes being affected are thus of some prognostic value in cancer of the breast, but the present inadequacy of knowledge of the behaviour of the disease makes accurate prediction of which patients will be cured impossible.

Introduction

Cancer of the breast, unlike many other forms of cancer, may recur or result in metastasis decades after the original diagnosis and treatment. Brinkley and Haybittle have, however, shown that the subgroup of women who remain free from the disease for 20 years after treatment have a subsequent survival that is similar to that of a normal population matched for age.[1] This suggests that the disease has been eradicated in most patients within this group. Nevertheless, despite the survival curves being apparently parallel, the women in the "cured" cohort still have a greatly increased risk of dying of breast cancer when compared with the normal population.

We analysed the records of all patients with clinically non-disseminated invasive cancer of the breast at first presentation who had received their primary treatment from this unit before 31 December 1961. Complete follow up was available for all these patients. Information was sought concerning the clinical and pathological features of each patient so that a comparison could be made between the group who survived for more than 20 years without recurrence or metastasis and those who died before this time. The object of the study was to identify those features observable at first presentation that predicted a favourable long term prognosis. In addition, the value of known "short term" prognostic indicators in predicting long term survival was also assessed.

Patients and methods

On reviewing the original histological slides we found that three survivors had had benign lesions (sclerosing papilloma, epithelial hyperplasia, and sclerosing adenosis). They were excluded from the study. We also excluded nine patients with in situ carcinomas. This left a total study population of 227 patients with histologically confirmed invasive breast cancer (tumour node metastasis (TNM) stages 1,2,3) who were treated in this unit from 1 January 1939 to 31 December 1961. From the unit's notes we sought age at diagnosis, duration of symptoms, stage and location of tumour, family history, method of treatment, duration of survival, and cause of death. In addition, details of menstrual state at diagnosis, marital state, and parity were obtained. Menstrual state was deemed to be unknown in those who had had a hysterectomy and were aged under 55. In patients who had survived 20 years the original pathological slides were reviewed to confirm the diagnosis, type the tumour, and grade the infiltrating ductal carcinomas, using the system devised by Bloom and Richardson.[2]

Standard life table methods were used in the analysis in addition to Student's t test and Yates's corrected χ^2 values for 2×2 tables. In life table analyses with three or more groups all χ^2 values are for trend across group and should be referred to the χ^2 distribution with one degree of freedom.[3,4] No allowance for natural mortality was made in computing expected values.

Results

Of the 227 patients, 51 (22%) survived for more than 20 years from the date of first treatment. Seven of these 51 patients, however, subsequently developed a recurrence or died of breast cancer more than 20 years after treatment. Of the 176 who died within 20 years, 26 had apparently done so from causes other than breast cancer without evidence of recurrence, but we did not attempt in the analyses below to separate these women from those who died of breast cancer.

As table I shows, more of the survivors at 20 years had had tumours at clinical stage 1 and a greater proportion of those who died had had lesions at stage 3 ($\chi^2=9{\cdot}16$; $p=0{\cdot}002$). Interestingly, however, 10 (20%) of the survivors had presented with stage 3 tumours. Most of the prognostic importance of clinical stage was associated with nodal state, and a more careful examination of this factor (fig 1 and table II) showed that clinical nodal state was an important predictor of survival to five years ($p<0{\cdot}0001$) but that it was of no value whatsoever after

TABLE I—*Clinical features at presentation of 51 patients who survived and 176 patients who died within 20 years after first treatment for breast cancer*

	Survived (n = 51)	Died (n = 176)
Mean age	47·7	53·2
No (%) with tumour at UICC stage:		
1	11 (21)	10 (6)
2	30 (59)	88 (50)
3	10 (20)	78 (44)
No (%) with tumour at pathological stage:		
1	30 (59)	39 (22)
2	18 (35)	86 (49)
3	3 (6)	51 (29)
No (%) with family history	5 (10)	22 (13)
No (%) with previous benign breast disease	3 (6)	18 (10)

Imperial Cancer Research Fund, Breast Cancer Unit, Guy's Hospital, London SE1 9RT

I S FENTIMAN, MD, FRCS, consultant surgeon
R R MILLIS, MB, MRCPATH, consultant pathologist
J L HAYWARD, FRCS, director

Imperial Cancer Research Fund, London WC2A 3PX

J CUZICK, PHD, staff scientist

Correspondence to: Mr I S Fentiman.

TABLE II—*Observed and expected deaths for different intervals of follow up for major prognostic factors. Expected values are those based on the log rank test and are not adjusted for natural mortality*

	0-5 years			5-10 years			10-20 years			>20 years			All periods		
	No	Deaths		No	Deaths		No	Deaths		No	Deaths		No	Deaths	
		Observed	Expected		Observed	Expected		Observed	Expected		Observed	Expected		Observed	Expected
Stage of tumour:															
1	23	3	13·35	20	4	8·17	16	4	6·54	12	4	4·60	23	15	32·89
2	115	42	58·74	73	24	25·65	49	19	16·68	30	11	10·47	115	96	112·09
3	42	23	17·67	19	8	6·45	11	3	3·98	8	4	2·92	42	39	31·21
4	47	37	15·24	10	7	2·72	3	2	0·81	1	0	1·01	47	46	19·81
χ^2 trend (p)	44·6 (<0·0001)			8·16 (0·003)			1·15 (0·14)			0·01 (0·53)			47·24 (<0·0001)		
Clinical nodal state:															
Negative	100	30	52·53	70	24	24·98	46	19	15·83	27	9	9·82	100	83	103·73
Positive	127	75	52·47	52	19	18·02	33	9	12·17	24	10	9·18	127	113	92·27
χ^2 trend (p)	19·66 (<0·0001)			0·09 (0·76)			1·46 (0·24)			0·15 (0·70)			8·95 (0·003)		
Age (years):															
-40	30	15	13·58	15	4	5·02	11	3	4·41	8	4	3·19	30	26	26·34
40-49	77	33	36·53	44	16	16·09	28	4	11·20	24	9	12·27	7	62	76·66
50-59	58	26	27·43	32	8	11·68	24	11	7·81	13	4	2·26	58	49	49·36
60-69	39	19	17·17	20	11	6·79	9	4	3·12	5	2	1·14	39	36	28·31
⩾70	23	12	10·28	11	4	3·42	7	6	1·46	1		0·14	23	22	15·33
χ^2 trend (p)	0·25 (0·31)			1·06 (0·15)			13·14 (0·0003)			0·48 (0·24)			5·32 (0·01)		

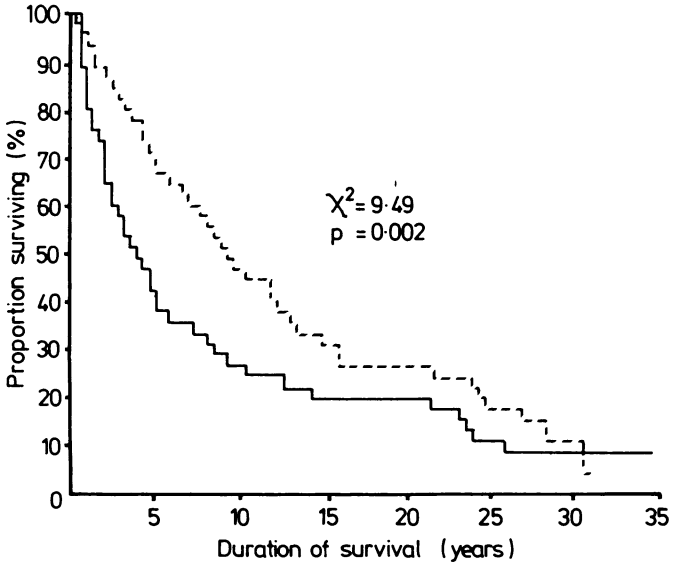


FIG 1—Life tables of patients with pathologically confirmed presence (127 patients (——)) and absence (99 patients (- - -)) of axillary lymph node metastases.

that. Thus the importance of clinical nodal state to long term survival resided in its ability to predict who would survive for the first five years.

A similar but less striking picture was seen when size of tumour was considered (fig 2 and table II). This also had a considerable effect in predicting survival in the first five years after diagnosis ($\chi^2=43$; $p<0·0001$). A smaller effect was seen from five to 10 years after first treatment ($\chi^2=8·16$; $p=0·0003$), and the association was no longer significant from 10 to 20 years ($\chi^2=1·15$; not significant) and was non-existent after 20 or more years ($\chi^2=0·01$; not significant).

A different pattern of time dependence was seen for age. At first presentation the average age of the survivors was 47·7 years compared with 53·2 for those who died within 20 years. The difference of 5·5 years was significant ($t=3·495$; $p=0·0007$). In contrast with nodal state and size of tumour, the effect of age became manifest only on long term follow up (fig 3, table II). Age at diagnosis had no material effect on survival in the first five years, a weak and non-significant effect after five to 10 years ($\chi^2=1·06$; $p=0·15$), but a strong effect after 10 to 20 years ($\chi^2=13·14$; $p=0·0003$). No further effect was seen after 20 years but this may have been due to the small numbers.

Results of histological examination of axillary lymph nodes were available for 48 (94%) of the survivors. Of these, 18 (35%) had had confirmed metastatic tumour within the lymph nodes. In contrast, axillary lymph node state was known in 125 of 133 women who had been treated by radical mastectomy and died within 20 years. Lymph nodes were pathologically affected in 86 (49%) of these 176 women ($\chi^2=12·90$; $p=0·0004$). This was almost certainly an underestimate of the number of women who died in whom axillary nodes were affected as in most patients not receiving radical mastectomy the nodes were irradiated and not removed because the tumours were advanced.

Of the survivors, five (10%) had a first degree relative with breast cancer compared with 22 (13%) of those who died ($\chi^2=0·08$; not significant), suggesting that a genetic predisposition did not enhance or diminish the probability of long term survival.

We assessed the effect of a history of previous breast surgery for non-malignant disorders. Preceding benign breast disease had been diagnosed in three survivors (6%) and 18 (10%) of those who died ($\chi^2=0·45$) and thus did not have a significant prognostic effect. Tables III, IV, V, and VI show, respectively, methods of treatment, duration of symptoms before first presentation to the clinic, location of primary tumours, and histological type and grade of tumour for those who survived and those who died within 20 years. None of these variables differed significantly between the two groups.

Of the patients who survived, 35 (69%) had been premenopausal at presentation compared with 71 (40%) of those who died ($\chi^2=11·6$; $p=0·0006$). When the survivors were subdivided, on the basis of their menopausal state, there was a similar distribution of clinical and pathological stages among those who were premenopausal and those who were postmenopausal. Furthermore, grades of tumour were similarly equally distributed between the two subgroups. Stages of tumour were also equally divided among premenopausal and postmenopausal women who died. Although premenopausal patients may develop tumours that are intrinsically less malignant, or possibly may mount a more effective host response to their tumours, the above

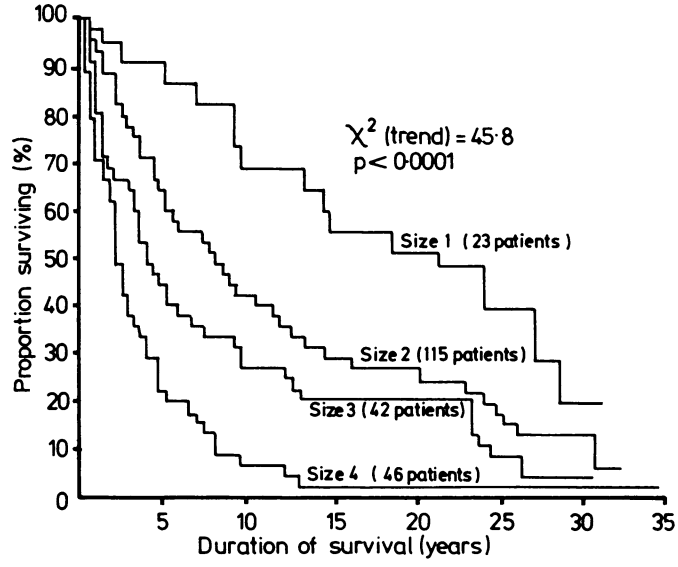


FIG 2—Life tables of patients subdivided by size (T_1, T_2, T_3, T_4) of tumour.

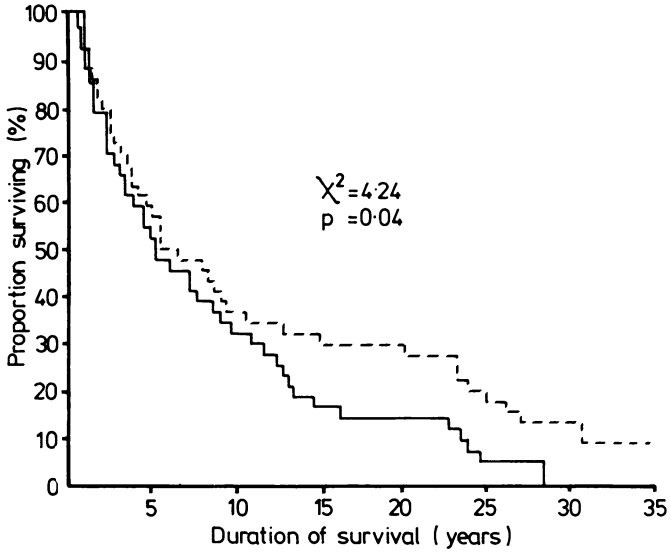


FIG 3—Life tables of 106 patients aged less than 50 (- - -) and 120 patients aged 50 or more at first presentation.

TABLE III—*Methods of treatment in patients who survived and patients who died within 20 years after first treatment for breast cancer*

	No (%) survived (n = 51)	No (%) died (n = 176)
Radical mastectomy	33 (65)	62 (35)
Radical mastectomy and postoperative deep *x* ray treatment	15 (29)	57 (32)
Preoperative deep *x* ray treatment and mastectomy	3 (6)	14 (8)
Simple mastectomy and deep *x* ray treatment		12 (7)
Wide excision and deep *x* ray treatment		5 (3)
Deep *x* ray treatment alone		26 (15)

TABLE IV—*Duration of symptoms before first presentation to clinic in 51 patients who survived and 176 patients who died within 20 years after first treatment for breast cancer*

Duration (months)	No (%) survived (n = 51)	No (%) died (n = 176)
<2	22 (43)	63 (36)
2-6	18 (35)	49 (28)
>6	11 (22)	59 (33)
Not known		5 (3)

TABLE V—*Location of primary tumour in 51 patients who survived and in 176 patients who died within 20 years after first treatment for breast cancer*

	No (%) survived (n = 51)	No (%) died (n = 176)
Medial	9 (18)	38 (22)
Lateral	27 (53)	82 (46)
Central	13 (25)	47 (27)
Diffuse	2 (4)	9 (5)

TABLE VI—*Histological type of tumours in 51 patients who survived and 176 patients who died within 20 years after first treatment for breast cancer. (Data not available for remaining 30 patients who died)*

	No (%) survived (n = 51)	No (%) died (n = 146)
Infiltrating ductal carcinoma	40 (78)	118 (81)
Grade 1	5 (13)	7 (4)
Grade 2	22 (55)	70 (60)
Grade 3	13 (32)	43 (36)
Infiltrating lobular carcinoma	6 (12)	16 (11)
Medullary carcinoma	3 (6)	2 (1·5)
Mucoid carcinoma	2 (4)	2 (1·5)
Other		8 (5)

differences in survival were more likely to have been due to natural mortality. Table VII shows that, among the survivors, 32 (63%) were parous as were 115 (65%) of those who died. For the group of nulliparous patients, 13 (68%) of the survivors were married compared with 30 (49%) of those who died. Lactation did not affect the prognosis: 27 (53%) of the survivors had breast fed as had 97 (55%) of those who died.

TABLE VII—*Reproductive features at presentation in 51 patients who survived and 176 patients who died within 20 years after first treatment for breast cancer*

	No (%) survived (n = 51)	No (%) died (n = 176)
Premenopausal	35 (69)	71 (40)
Postmenopausal	16 (31)	99 (56)
Unknown		6 (4)
Parous	32 (63)	115 (65)
Nulliparous	19 (37)	61 (35)
Married nulliparous	13 (26)	30 (17)
Lactation	27 (53)	97 (55)

A second primary tumour developed in the contralateral breast of six (12%) of the survivors, five of whom died of metastatic breast cancer more than 20 years after first treatment.

Discussion

Our study showed that 51 (22%) of this unit's patients with clinically localised invasive breast cancers survived for 20 years from the time of diagnosis. Their survival was not related to the site of the tumour, duration of symptoms, previous benign breast disease, family history, parity, or lactation. Although size of tumour and axillary nodal state were significant prognostic variables, their contribution was almost completely confined to prediction of survival for five years. Thereafter, these variables did not affect survival, so that one quarter of the long term survivors had tumours greater than 5 cm in diameter and one third had pathologically affected axillary nodes. In addition, grade of tumour did not appear to be a long term prognostic indicator as 13 (25%) of the survivors had grade 3 infiltrating ductal carcinomas compared with 43 (24%) of those who died.

The age and menstrual state of the patient at presentation had a prognostic value independent of tumour stage and grade. Although premenopausal patients may develop tumours that are intrinsically less malignant or possibly mount a more effective response to their tumour, these differences were more likely to have been due to natural mortality, as the importance of age manifests itself 10 years or more after the initial diagnosis. Similar findings were reported in the studies of Langlands and Kerr[5] and of Pocock *et al*,[6] who analysed the survival of 3878 patients treated by simple mastectomy and radiotherapy. When cases were subdivided by clinical stage and size of tumour there was a non-proportional hazard with time, resulting in a decay of the prognostic ability of clinical stage.

Our findings refute the hypothesis that there are two distinct variants of breast cancer—namely, one that remains locally invasive and another that metastasises and is therefore incurable[7]—as 18 (35%) of our survivors had had histologically confirmed axillary metastases. Adair also reported a 30% incidence of axillary nodes being affected in cured patients.[8] Trials of aggressive treatment to the axilla either by surgery or radiotherapy do not, however, suggest that this substantially affects survival, at least over the short term.

None of the survivors had received any form of systemic adjuvant treatment—that is, no attempt had been made to destroy putative micrometastases. The non-appearance of clinical metastases during the ensuing 20 years of complete follow up suggested that axillary metastases were not invariably associated with dissemination of disease. Based on our figures, if entry to trials of adjuvant cytotoxic chemotherapy had been dictated by the presence of axillary node metastases (found in

104 of the 173 patients for whom histological data were available) 18 patients (17%) would have received unnecessary treatment. In contrast, of the 69 patients known to have had unaffected axillary nodes 39 (57%) died in the subsequent 20 years.

Interestingly, five (10%) of the so called "cured group" died of metastases after developing contralateral breast cancer more than 20 years after first treatment. Although there is no firm evidence to support this, many late deaths from breast cancer may possibly be the result of new tumours rather than a late manifestation of slow growing micrometastases.

Our results indicate that, although age, menstrual state, clinical stage, and spread to axillary nodes are of some prognostic value in breast cancer, the present inadequacy of knowledge of the behaviour of the disease makes accurate prediction of which patients will be cured impossible.

We thank Miss P Latter for her excellent technical and clerical help.

References

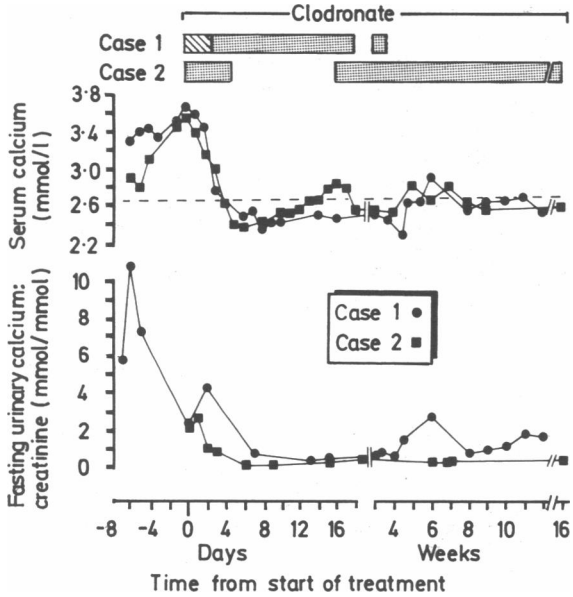
1 Brinkley D, Haybittle JL. The curability of breast cancer. *Lancet* 1975;ii:95-6.
2 Bloom HJG, Richardson WM. Histological grading and prognosis in breast cancer. *Br J Cancer* 1957;**11**:359-77.
3 Peto R, Pike MC, Armitage P, *et al*. Design and analysis of randomised trials which require prolonged observations of each patient. I. *Br J Cancer* 1976;**34**:585-612.
4 Peto R, Pike MC, Armitage P, *et al*. Design and analysis of randomised trials which require prolonged observations of each patient. II. *Br J Cancer* 1977;**35**:1-39.
5 Langlands AO, Kerr GR. Prognosis in breast cancer: the effect of age and menstrual status. *Clin Oncol* 1979;**5**:123-33.
6 Pocock SJ, Gore SM, Kerr GR. Long term survival analysis: the curability of breast cancer. *Statistics in Medicine* 1982;**1**:93-104.
7 McKinnon NE. Control of cancer mortality. *Lancet* 1954;i:251-4.
8 Adair F, Berg J, Joubert L, Robbins GE. Long term follow-up of breast cancer patients: the 30 year report. *Cancer* 1974;**30**:1145-50.

(*Accepted 26 July 1984*)

SHORT REPORTS

Immobilisation hypercalcaemia in adults and treatment with clodronate

Hypercalcaemia is a recognised complication of prolonged immobilisation. It occurs in patients with high rates of bone turnover, including children and adolescents,[1] and is thought to be due to an increase in net bone resorption.[2] In adults severe immobilisation hypercalcaemia is rare, but milder degrees may be more common than hitherto recognised.[3] We report two cases.



Biochemical values in two patients before and during treatment of immobilisation hypercalcaemia. Stippled area indicates oral treatment with clodronate (1·6 g daily) and hatched area intravenous treatment (100 mg daily).

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

Case reports

Case 1—A 43 year old woman developed severe, widespread flaccid paralysis over 36 hours due to acute fulminating postinfective polyneuritis. Assisted ventilation was required for 23 weeks. After 11 months she had regained grade III power in the proximal leg muscles, but she then developed malaise, nausea, and vomiting and became dehydrated. Serum calcium concentration was raised at 3·92 mmol/l (15·7 mg/100 ml), fell transiently after treatment with intravenous saline, but rose again to 3·66 mmol/l (14·6 mg/100 ml) despite continuous rehydration for 19 days.

Case 2—A 32 year old woman underwent renal transplantation three months before presentation. Radiographs and serum alkaline phosphatase activity showed no evidence of bone disease, but 14 months previously she had received 1α-hydroxycholecalciferol for hyperparathyroid bone disease. Renal function was stable (creatinine clearance 38 ml/min), and immunosuppression was maintained with azathioprine and prednisolone. One month after transplantation she developed cough and dyspnoea, subsequently attributed to cytomegalovirus infection, and required assisted ventilation for four weeks. She then developed a generalised grade II limb weakness due to a peripheral motor neuropathy. Power returned gradually over the subsequent two months, but serum calcium concentration rose to 3·54 mmol/l (14 mg/100 ml) despite adequate hydration and treatment with prednisolone (10 mg daily).

In both patients serum immunoreactive parathyroid hormone was undetectable (< 40 pg/ml) and the concentration of 1,25-dihydroxycholecalciferol was low (21 pmol/l (8·2 pg/ml) and 42 pmol/l (16·9 pg/ml) respectively; normal 45-138 pmol/l (18-55 pg/ml)). Both patients had biochemical evidence of increased bone resorption as judged by high ratios of fasting urinary calcium to creatinine concentrations (figure) and of hydroxyproline to creatinine concentrations (374 and 83·3 mmol/mol (434 and 97 mg/g) respectively (normal 10-30 mmol/mol (12-35 mg/g)). Both patients were treated with clodronate and became normocalcaemic within five days (figure). When treatment was stopped after five days in case 2 the hypercalcaemia recurred, but it responded to further treatment. Fasting urinary calcium excretion, initially high in both patients, fell to normal within two weeks after the start of treatment. In case 1 both serum calcium concentration and fasting urinary calcium excretion rose transiently when clodronate was stopped after one month of treatment. Urinary hydroxyproline excretion was initially unchanged but fell gradually to normal after three months in both patients.

Comment

It is not clear whether the increasing mobility of our two patients may in some way have triggered their hypercalcaemia. Serum concentrations of 1,25-dihydroxycholecalciferol were low, suggesting that intestinal absorption of calcium was also low. The undetectable concentrations of immunoreactive parathyroid hormone excluded hyperparathyroidism as a cause for the hypercalcaemia.

Both patients had biochemical evidence of increased bone resorption, and in both creatinine clearance was impaired. Impairment of renal function would not cause, but is likely to contribute to, hypercalcaemia, and in both cases appreciable bone resorption appeared to be the major mechanism for hypercalcaemia. These conclusions are supported by the response of these patients to clodronate. This agent has been previously used in Paget's disease and hypercalcaemic disorders associated with increased bone resorption.[4] The effects of clodronate in immobilisation hypercalcaemia have not been reported previously, although the drug inhibits bone loss after immobilisation in experimental animals and in paraplegia. Plasma calcium concentration and fasting urinary calcium excretion decreased in both our patients, indicating the efficacy of treatment. The diphosphonate etidronate is also effective,[5] but its action to