

STUDIES OF CALCIUM METABOLISM IN MULTIPLE MYELOMA WITH CALCIUM⁴⁷ AND METABOLIC-BALANCE TECHNIQUES

BY MICHAEL Z. LAZOR,* LEON ROSENBERG,† AND PAUL CARBONE

(From the Radiation Branch, Metabolism Service and Medicine Branch,
National Cancer Institute, Bethesda, Md.)

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Despite the fact that approximately 90% of patients with multiple myeloma present themselves with skeletal complaints (1, 2), few studies of bone mineral metabolism in this disease have been reported. Stable calcium studies in multiple myeloma were first reported in the literature by Blatherwick (3) in 1916. Since that time there have been only infrequent reports using balance techniques, or isotopic-tracer methods, or both. Adams, Mason, and Bassett (4) used metabolic-balance techniques to investigate the influence of ACTH on mineral metabolism in three patients with multiple myeloma. Case studies of one or two patients using tracer methods and balance techniques have been reported by Anderson, Emery, McAllister, and Osborn (5), after a therapeutic dose of Ca⁴⁵; by Spencer, Li, Samachson, and Laszlo (6), who have studied the comparative excretion and retention of Sr⁸⁵ and Ca⁴⁵; and recently, by Skoog, Adams, and MacDonald (7), who have reported balance and Sr⁸⁵-tracer studies in a patient with multiple myeloma treated with various combination of hormones.

The study of calcium metabolism in multiple myeloma is of great interest, since diffuse osteoporosis, or osteolytic lesions, or both, are most always present, and hypercalcemia is a frequent (8) but poorly understood complication. With the increasing availability of clinically suitable radioactive isotopes of calcium, calcium-balance measurements can now be supplemented with kinetic-tracer studies. Stable calcium-balance studies alone measure only the net difference between bone formation and resorption. With Ca⁴⁷-tracer studies in addition to balance techniques, calcium absorption, endogenous fecal calcium, exchangeable or miscible calcium, and miscible cal-

cium turnover rates can be estimated. The present report describes studies of calcium metabolism using Ca⁴⁷ and balance techniques in six patients with multiple myeloma. These studies indicate that the gut is an important source of calcium loss in multiple myeloma, and that the endogenous fecal calcium contributes significantly to the negative calcium balance uniformly found in our patients.

MATERIALS AND METHODS

Patients. Three men and three women with multiple myeloma were studied. Their ages ranged from 44 to 65 years. All patients were ambulatory during the entire study. The diagnosis of multiple myeloma was established by abnormalities in serum-protein pattern, bone-marrow examination, and skeletal X rays consistent with that disease. Serum calcium, phosphorus, and alkaline phosphatase were within normal limits in each patient (Table I). The term "untreated," as used in this patient population, refers to the absence of systemic treatment during the 3 months before study.

Metabolic balance. All patients were studied in a metabolic-balance ward while they were maintained on fixed metabolic-balance diets, analyzed in triplicate. Four patients received approximately 200 mg Ca and 800 mg P daily, and two received approximately 500 mg Ca and 1,000 mg P daily. All patients were maintained on the specified diets for 8 to 10 days before the balance studies to allow for equilibration to the low-calcium diet and to the metabolic routine. Refused food and emeses were saved, analyzed, and subtracted from the daily intake for that period. Fluid intake was kept constant by providing a fixed quantity of distilled water daily. Voided urine specimens were immediately pooled in a refrigerated jar containing 10 ml of concentrated HCl. Stools were separated at intervals of 4 days with carmine markers. The following analytical methods were used: nitrogen, macro-Kjeldahl (9); urinary, fecal, and dietary phosphorus, Taussky and Shorr (10); serum phosphorus, Reiner (11); urinary, fecal, and dietary calcium, Kochakian and Fox (12); and serum calcium, MacIntyre (13). Daily urine samples were analyzed for nitrogen. Sample of 4-day pooled stools were analyzed for calcium, phosphorus, and nitrogen.

Intravenous Ca⁴⁷ studies. All patients were given 30 μ Ci Ca⁴⁷Cl₂ intravenously before breakfast in 10 ml of iso-

* Present address: Hartford Hospital, Hartford, Conn.

† Present address: Grace-New Haven Hospital, New Haven, Conn.

TABLE I
Clinical and laboratory data in six patients with multiple myeloma

Subject	Wt kg	Age years	Sex	Dura- tion of myeloma months	Serum proteins		Alkaline phos- phatase King- Arm- strong U	Serum Ca mg/ 100 ml	Serum phos- phorus mg/ 100 ml	Blood urea nitrogen mg/ 100 ml	Bone marrow	Skeletal X rays	Therapy
					Total	A/C*							
LE	65	64	F	15	9.7	3.3/6.4	8	9.5	4.3	18	Many plasma cells	Single lytic lesion, left frontal bone; diffuse osteoporosis	Received placebo while on urethane protocol 10 months before study
OT	69	61	M	2	11.1	3.2/7.9	7	9.2	4.0	19	Replaced by plasma cells	Compression T7 and 9; diffuse osteoporosis	X ray to thoracic spine 1 month before admission.
NS [1]	65	44	M	22	13.0	2.5/10.5	8	9.8	3.5	15	Plasma cells, 25%	Very extensive osteolytic lesions; compression T7, 8, 11, and L1; diffuse osteoporosis	None
NS [2]	65	44	M	25	13.0	2.5/10.5	9	8.7	2.5	15	Plasma cells, 5 to 30%	Unchanged from the first study	5-Fluorouracil during admission
RF	76	65	M	1	9.2	2.9/6.3	8	10.2	3.9	22	"Almost all cells are plasma cells"	Extensive osteolytic lesions involving skull, humerus, and ribs; compression fracture T7; diffuse osteoporosis	X ray to spine 1 month before study
AS	65	65	F	5	11.8	2.2/9.6	5	9.2	3.5	17	Plasma cells, 40%	Diffuse osteoporosis	None
HK	62	53	F	24	9.0	3.6/5.4	8	10.0	4.5	14	Plasma cells, 98%	Minimal osteolytic involvement of ribs and pelvis; diffuse osteoporosis	Urethane and X ray to spine 21 months before study; Vincristine 3 months before study.

* Albumin/globulin ratio.

tonic saline, except patient LE, who received $15 \mu\text{c}$. Ca^{47} has a half-life of 4.7 days and emits a high-energy gamma ray of 1.3 Mev as well as a beta particle in its decay to scandium 47 (14). The Ca^{47} specific activity on receipt from Union Carbide Corporation in Oak Ridge, Tennessee, was approximately 200 mc per g. All counting was done in a single-channel gamma-ray spectrometer, with the lower gate set at 400 Kev to exclude Sc^{47} . Two-ml serum samples were counted in an automatic well-type scintillation counter. Five-hundred-ml samples of daily urine and 500-ml samples of homogenized, 4-day pooled stools were counted in 1-quart paint cans over a 2-inch NaI crystal of a well-type gamma counter. Samples of the original Ca^{47} solution were also counted, and the results of the biological samples were expressed as fractions or percentages of administered dose. All samples were counted sufficiently long to insure statistical counting errors of less than 5%.

Oral Ca^{47} studies and calcium absorption. Three patients, AS, HK, and NS, were given Ca^{47} orally as well

as intravenously. The oral isotope was administered 7 to 10 days before the intravenous Ca^{47} in all cases. One μc of Ca^{47} was given orally in distilled water while the patient was eating breakfast. All stools were counted until activity returned to background, an interval varying from 5 to 10 days. The fractions of dietary calcium and Ca^{47} absorbed are assumed to be identical, assuming that Ca^{47} and stable calcium are completely mixed before absorption, and that neither isotope is absorbed preferentially. Absorbed dietary calcium (milligrams per day) was calculated from Equation 1 by determining the fraction of oral Ca^{47} not absorbed: *calcium absorption* = $(1 - fs') \times \text{dietary calcium}$, where fs' = fraction of orally administered Ca^{47} that is not absorbed. Calcium absorption was also calculated from the intravenous Ca^{47} data by the following relationships: a) total fecal calcium = unabsorbed dietary calcium + endogenous fecal calcium and b) dietary calcium = unabsorbed dietary calcium + absorbed dietary calcium. The total fecal calcium and the dietary calcium were determined by the

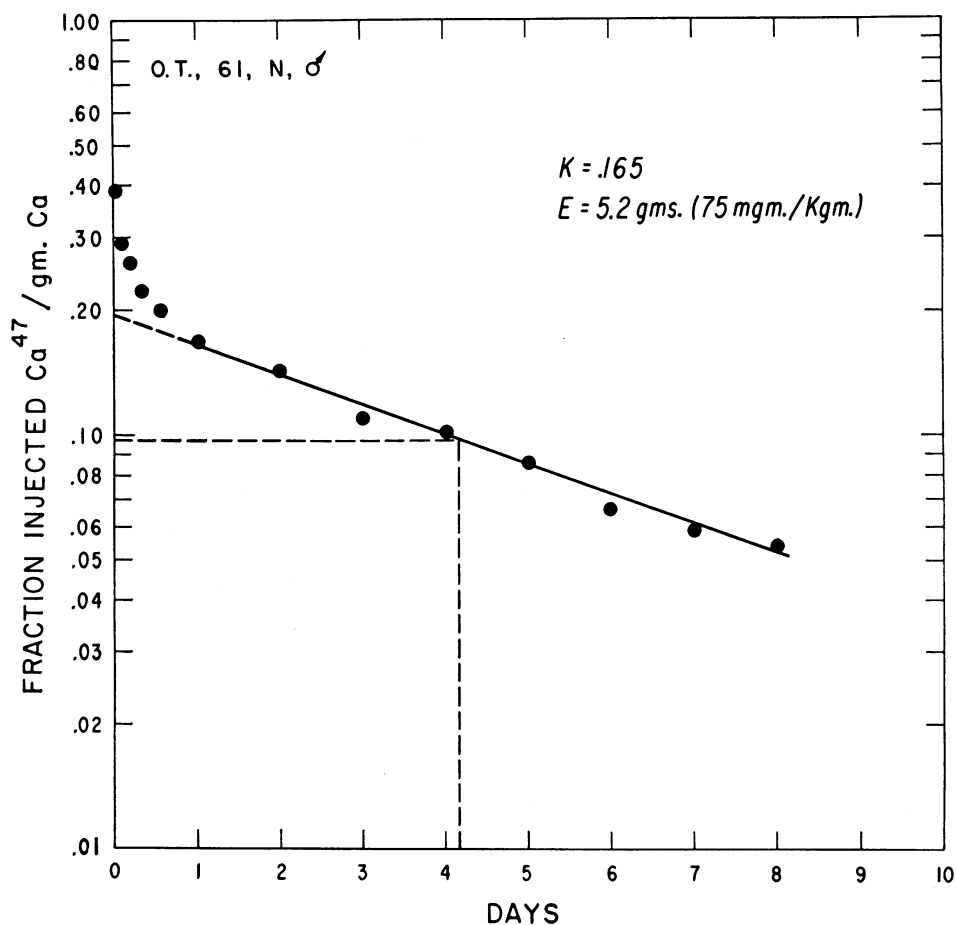


FIG. 1. SERUM SPECIFIC ACTIVITY IN PATIENT OT AFTER THE IV INJECTION OF Ca^{47} . The final exponential is extrapolated to the ordinate at zero time to determine E. The $t_{1/2}$ (4.2 days) is the interval during which the serum specific activity falls to one-half of its value at zero time. K then = $\ln 2/t_{1/2}$.

analytical methods of Kochakian and Fox (12). The endogenous fecal calcium was determined by Equation 2 described below. Relationship *a*) can then be solved for unabsorbed dietary calcium, which is substituted in relationship *b*) to determine the absorbed dietary calcium.

Endogenous fecal calcium. Endogenous fecal calcium is defined as the calcium secreted into the gut (total digestive-juice calcium) minus the absorbed secreted cal-

cium. The following relationship, Equation 2, was used to estimate the endogenous fecal calcium (milligrams per day): *endogenous fecal calcium* = $(U_{Ca}/\Delta t) \times fs/fu$, where Δt = entire period Ca^{45} is followed in the urine and stool, U_{Ca} = urinary stable Ca in milligrams during Δt , fs = fraction of intravenously administered Ca^{45} in stool during Δt , and fu = fraction of intravenously administered Ca^{45} in urine during Δt .

TABLE II
Metabolic balance of calcium, phosphorus, and nitrogen

Subject	4-Day periods	Calcium			Phosphorus				Nitrogen				
		Intake	Urine	Feces	Balance	Intake	Urine	Feces	Balance	Intake	Urine	Feces	Balance
	no.	g/day			g/day				g/day				
LE	1	.212	.033	.264	-.085	.774	.539	.331	-.096	11.09	9.26	1.21	+0.62
	2	.212	.032	.357	-.177	.774	.446	.443	-.115	11.09	8.87	1.54	+0.68
	3	.212	.025	.382	-.195	.774	.433	.483	-.142	11.09	9.03	1.73	+0.33
	4	.212	.021	.346	-.155	.774	.435	.425	-.086	11.09	9.61	1.40	+0.08
	5	.212	.015	.322	-.125	.774	.443	.426	-.095	11.09	9.65	1.43	+0.01
	Average		.212	.025	.335	-.148	.774	.459	.422	-.107	11.09	9.28	1.46
OT	1	.205	.120	.337	-.252	.766	.522	.214	+.030	9.78	10.61	1.48	-2.31
	2	.205	.110	.290	-.195	.766	.667	.202	-.103	9.78	9.55	1.20	-0.97
	3	.205	.093	.372	-.260	.766	.636	.251	-.121	9.78	9.92	1.46	-1.60
	4	.205	.111	.334	-.240	.766	.559	.221	-.014	9.78	9.52	1.29	-1.03
	5	.205	.093	.350	-.238	.766	.557	.232	-.023	9.78	9.44	1.33	-0.99
	Average		.205	.105	.337	-.237	.766	.588	.224	-.046	9.78	9.81	1.35
NS [1]	1	.212	.319	.340	-.447	.868	.759	.273	-.164	11.67	10.44	1.56	-0.33
	2	.212	.258	.456	-.052	.868	.699	.368	-.199	11.67	9.22	1.63	+0.82
	3	.212	.245	.454	-.487	.868	.805	.300	-.237	11.67	9.24	1.71	+0.72
	4	.212	.266	.330	-.384	.868	.752	.238	-.122	11.67	8.62	1.18	+1.87
	Average		.212	.272	.395	-.455	.868	.754	.295	-.181	11.67	9.38	1.52
NS [2]	1	.214	.091	.548	-.425	.862	.745	.476	-.359	11.52	12.29	2.28	-3.05
	2	.214	.078	.265	-.129	.862	.842	.232	-.212	11.52	12.19	1.05	-1.72
	3	.114	.073	.753	-.612	.862	.759	.600	-.497	11.52	12.11	2.95	-3.54
	4	.214	.076	.522	-.384	.862	.790	.319	-.247	11.52	12.06	2.11	-2.65
	Average		.214	.080	.522	-.388	.862	.784	.407	-.329	11.52	12.16	2.10
RF	1	.212	.272	.220	-.280	.873	1.025	.202	-.354	14.43	13.88	0.77	+0.28
	2	.212	.283	.387	-.458	.873	1.096	.351	-.574	14.43	15.02	1.15	-1.74
	3	.212	.265	.433	-.486	.873	.922	.396	-.445	14.43	12.83	1.68	-0.08
	4	.212	.261	.262	-.311	.873	.740	.239	-.106	14.43	12.13	1.20	+1.10
	5	.212	.250	.433	-.471	.873	.787	.426	-.340	14.43	11.81	1.74	+0.88
	Average		.212	.266	.347	-.401	.873	.941	.323	-.364	14.43	13.02	1.31
AS	1	.511	.161	.528	-.178	.958	.590	.216	+.152	12.27	6.56	1.24	+4.47
	2	.511	.131	.644	-.264	.958	.467	.209	+.281	12.27	6.72	1.60	+3.94
	3	.511	.179	.538	-.206	.958	.620	.356	-.018	12.27	7.31	1.42	+3.54
	4	.511	.172	.620	-.281	.958	.690	.405	-.137	12.27	6.26	1.56	+4.44
	5	.511	.184	.599	-.272	.958	.718	.383	-.143	12.27	7.55	1.94	+2.77
	Average		.511	.165	.586	-.240	.958	.617	.314	+.027	12.27	6.88	1.56
HK	1	.530	.061	.507	-.038	1.148	.807	.390	-.049	13.09	12.54	1.09	-0.54
	2	.530	.074	.515	-.059	1.148	.715	.400	+.033	13.09	11.70	1.32	+0.07
	3	.530	.068	.576	-.114	1.148	.750	.432	-.034	13.09	11.76	1.35	-0.02
	4	.530	.077	.526	-.073	1.148	.801	.414	-.067	13.09	11.21	1.27	+0.61
	5	.530	.080	.621	-.171	1.148	.801	.438	-.091	13.09	11.46	1.50	+0.13
	6	.530	.081	.584	-.135	1.148	.759	.417	-.028	13.09	11.22	1.30	+0.58
	7	.530	.071	.527	-.068	1.148	.744	.367	+.037	13.09	11.20	1.25	+0.64
	8	.530	.078	.452	.000	1.148	.749	.338	+.061	13.09	11.16	1.16	+0.77
	Average		.530	.074	.538	-.082	1.148	.766	.400	-.018	13.09	11.53	1.28

TABLE III
*Estimation of calcium absorption and endogenous fecal calcium after oral, or intravenous Ca⁴⁷, or both**

Subject	Intake	Absorbed	Unabsorbed	Endogenous fecal	Total fecal
	<i>mg/day</i>	<i>mg/day</i>	<i>mg/day</i>	<i>mg/day</i>	<i>mg/day</i>
LE	210			>125†	335
OT	205	25 iv	180 iv	155 iv	335
NS [1]	210	150 iv	60 iv	335 iv‡	395
NS [2]	215	5 p.o. -15 iv	210 p.o. 230 iv	310 p.o. 290 iv	520
FR	210	85 iv	125 iv	220 iv	345
AS	510	185 p.o. 165 iv	325 p.o. 345 iv	260 p.o. 240 iv	585
HK	530	105 p.o. 120 iv	425 p.o. 410 iv	115 p.o. 120 iv	540

* Values indicated by "iv" were determined from intravenous Ca⁴⁷ data, and those by "p.o.," from oral Ca⁴⁷ data.

† Estimated from difference between total fecal calcium and intake.

‡ Estimated from 4-day stool collection.

After intravenous Ca⁴⁷, radioactivity appeared in the urine within minutes, whereas radioactivity was not detected in the stool for 12 to 48 hours. To count cumulative activity in urine and stool for an identical interval (Δt), the stool was monitored for an additional period, corresponding to this lag. For example, if no stool radioactivity was detectable for 24 hours, the urine activity would be monitored from days 1 to 7, while stool activity would be determined for days 2 to 8.

Calcium kinetics. The conceptual model employed to determine the miscible calcium pool (E) and "bone-formation rate" ("BFR") was that of Heaney and Whedon (15). The miscible calcium pool was determined by extrapolating the exponential portion of the serum specific activity curve to zero time and dividing the administered dose by the specific activity at zero time. An example of the exponential phase used in these studies is shown in

Figure 1. "Bone-formation rates" were calculated by the formula proposed by Heaney and Whedon (15): $BFR = EK(1 - fu^\infty - fs^\infty)$, where E = miscible calcium pool, K = fractional rate of loss of isotope by all routes from pool E , fu^∞ = fraction of intravenously administered Ca⁴⁷ excreted in urine, and fs^∞ = fraction of intravenously administered Ca⁴⁷ excreted in stool. (Quotation marks are used because the evidence is not convincing that bone-formation rate alone is being measured).

RESULTS

Balance studies. As shown in Table II, all untreated patients were in positive nitrogen-balance equilibrium, except OT. Studies I and II of NS will be discussed below under a separate heading.

TABLE IV
Estimation of miscible calcium pool and "bone-formation rate" after intravenous Ca⁴⁷

Subject	Cumulative Ca ⁴⁷ excretion						"Bone-formation rate"
	E*	K†	Urine	Days counted	Stool	Days counted	
	<i>mg/kg</i>		<i>% injected dose</i>		<i>% injected dose</i>		<i>mg/kg/day</i>
LE	90	.084	1.7	3‡	5.2	2	5.7
OT	75	.164	9.5	7	13.8	7	10.6
NS [1]	70	.209	20.0	6	9.2§	4	12.1
NS [2]	103	.235	4.6	6	16.9	6	23.2
RF	53	.165	22.7	7	19.1	7	7.1
AS	98	.186	6.7	6	9.7	6	16.8
HK	73	.169	5.6	6	9.6	6	11.4
Normal values (15)	60-110						8-11

* Miscible calcium pool.

† Disappearance constant. See legend of Figure 1 for the derivation of K.

‡ Unable to follow beyond 3 days, since patient had low urinary calcium and only 15 μ c Ca⁴⁷ injected.

§ First 2 days' stool not counted.

All patients were in negative phosphorus balance or equilibrium. Calcium balance was distinctly negative in all patients, while they were ingesting 200 mg or 500 mg calcium per day (Table II). As can be seen from Tables I and II, the magnitude of the negative calcium balance, ranging from 90 to 455 mg per day, could be correlated with the severity of the skeletal involvement as judged by X-ray bone surveys. There was little fluctuation in the calcium excretion during the balance studies, as noted in Table II. Serum calcium and body weights were stable during the balance studies.

Absorbed dietary calcium. Calcium absorption, with oral Ca⁴⁷, was determined in NS, AS, and HK. In HK, the absorption study was repeated after 7 days with excellent agreement (16 and 22%). Estimates of calcium absorption for these patients, as well as for OT, NS, and RF were also obtained indirectly from the interrelationships given above after intravenous Ca⁴⁷. As can be seen from Table III, calcium absorption varied from 12 to 70%. All values in Table III have been rounded off to the nearest 5 mg.

Endogenous fecal calcium. In all patients except RF, the endogenous fecal calcium exceeded the urinary calcium excretion (Tables II and III). Endogenous fecal calcium was determined in patients NS, AS, and HK by both the intravenous and oral-tracer methods as described above. As Table III shows, the results obtained by the oral and intravenous methods are in excellent agreement. There appeared to be a distinct correlation between endogenous fecal calcium and total urinary calcium excretion (correlation coefficient = 0.862), but sample size is admittedly small.

Miscible calcium pool and Ca⁴⁷ disappearance from serum. Figure 1 shows a representative disappearance curve after intravenous administration of 30 μ c Ca⁴⁷. In all patients except LE, the rate of disappearance of intravenous calcium label was found to be more rapid than in a group of normal control volunteers and patients with senile osteoporosis (15, 16). Despite the increased values for K, the estimates of the miscible calcium pool E were normal, except for patient RF, in whom it was reduced (Table IV). The abnormally rapid disappearance of intravenously administered labels in those patients with normal bone-formation rates was explained by the exces-

sive excretion of isotope in urine and stool. All values for the "bone-formation rates" were essentially within normal limits, except for LE and AS, in whom values were reduced and elevated, respectively.

Patient NS. This patient strikingly demonstrated the importance of determining the total fecal calcium and its fractions. The data from NS, presented in detail in Figure 2, were of particular interest in that the studies revealed marked differences in the gastrointestinal and renal handling of calcium before and during 5-fluorouracil therapy. During the pretreatment study, the patient was in marked negative calcium balance. Absorption of dietary calcium while he was on a 210-mg calcium diet was approximately 70% (Table II). The endogenous fecal calcium was 335 mg per day, and the urinary calcium excretion, 270 mg per day. He then received a total of 33 g of 5-fluorouracil over 76 days, beginning approximately 60 days before the second study. When restudied after 80 days, calcium absorption was virtually zero (Table II), when measured with either oral or intravenous Ca⁴⁷. The endogenous fecal calcium was 290 mg per day, and the urinary calcium was markedly lower (80 mg per day) than during the pretreatment study. Without tracer Ca⁴⁷ studies, the profound effect of 5-fluorouracil on calcium absorption would not have been apparent. If urinary calcium alone were followed, as suggested by Meyers (17), a beneficial effect on bone mineral metabolism would have been assumed. An explanation for the increased "bone-formation rate" in the second study is not apparent. The marked negative calcium balances during both studies, however, indicate bone resorption in excess of bone formation. The increased fecal nitrogen, as well as the decreased calcium absorption during 5-fluorouracil therapy, is consistent with this drug's cytotoxic effect on the mucosa of the small intestine.

DISCUSSION

Contrary to findings in normal subjects (18), the endogenous fecal calcium was greater than the urinary calcium in five of the six patients with multiple myeloma studied. This observation is especially significant since considerable controversy still exists regarding the importance of the gastrointestinal tract in endogenous calcium excretion.

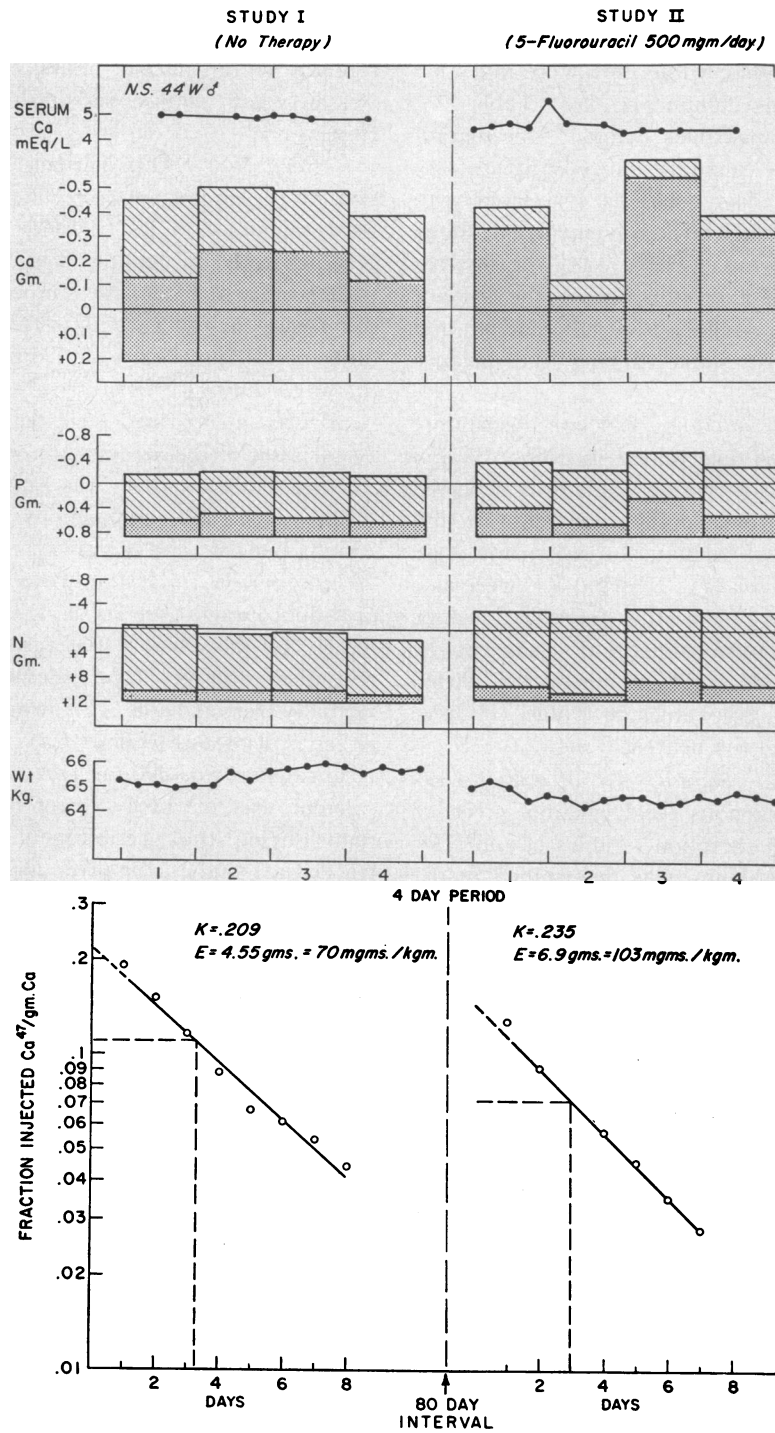


FIG. 2. METABOLIC-BALANCE GRAPHS AND Ca^{47} SERUM DISAPPEARANCE STUDIES BEFORE AND DURING 5-FLUOROURACIL THERAPY. In the balance graphs, intake is plotted downward from the zero line. Fecal (stippled area) and urinary values (cross-hatched area) are plotted upward. E and K are determined as in Figure 1.

It has only been with the availability of Ca⁴⁵ and Ca⁴⁷ that endogenous fecal calcium could be approximated in a patient. Brine and Johnston (19) plotted fecal calcium against dietary calcium from 51 balance studies in the literature, and extrapolated the intake to zero. In this way, the endogenous fecal calcium was estimated to be 75 mg per day. Subsequently, endogenous fecal calcium has been studied in various diseases with radioactive calcium isotopes (20–23). Although endogenous fecal calcium has never been measured in multiple myeloma, Anderson and colleagues (5) reported a total digestive-juice calcium of 465 mg per day, with very wide daily fluctuations, in a single patient with this disease.

Initially in this study, the endogenous fecal calcium was calculated by the method of Comar, Monroe, Visek, and Hansard (24), relating total fecal isotopic activity to serum specific activity. This method assumes that the specific activity of the stool calcium follows that of the blood, but 24 hours later. Because preliminary observations with this technique yielded unsatisfactory results, the method described above was used. Aubert and Milhaud (25) and Bronner (26) have recently suggested a very similar method to determine endogenous fecal calcium. From oral Ca⁴⁷-tracer studies, a second, indirect value for endogenous fecal calcium, as well as a value for absorbed dietary calcium, was obtained. In patients NS, AS, and HK, the results for endogenous fecal calcium and absorbed dietary calcium, by the oral and intravenous-tracer methods, were in excellent agreement (Table III).

As Bronner recently pointed out (26), the factors determining endogenous fecal calcium are largely unknown. In our study, there appears to be no correlation with serum calcium, miscible calcium-pool size, or the dietary calcium levels used. There appeared to be a distinct correlation between endogenous fecal calcium and total urinary calcium (correlation coefficient = 0.862), but the population sample was admittedly too small to make this statistically significant, and more data are needed.

There have been several studies of calcium metabolism in malignant disease in which fecal calcium excretion has not been reported (27–29). Meyers (17) has stated that “decreases in serum and urinary calcium are not the result of increases

in fecal calcium.” Our results with patient NS contradict this observation. In a recent metabolic-balance and Sr⁸⁵-tracer study in a patient with multiple myeloma, Skoog and co-workers (7) claimed that Sr⁸⁵-excretion studies “emphasize the now known fact that endogenous calcium excretion is largely renal.” Our studies as well as those quoted above (20–23) indicate that the gastrointestinal tract is a very significant route for endogenous calcium excretion. The multiple variables (30) influencing the preferential absorption of calcium over strontium preclude a simple extrapolation for calcium absorption, gut secretion, and urinary excretion from the strontium data alone.

Low-calcium diets were used for two reasons: to note small fluctuations in calcium balance that would be more apparent on the low intake than on a high-calcium diet, and to obviate the need for a change in calcium if one of the subjects studied became hypercalcemic. It has been known for many years (31) that normal controls on low-calcium diets (less than 300 mg daily) persistently show a negative calcium balance of approximately 100 mg per day. Very similar results have been shown more recently (20, 32). In all of our patients, the negative calcium balance exceeded the value expected with the low-calcium intakes alone. These results are consistent with previously reported calcium-balance studies in myeloma patients on various calcium intakes (1, 2, 3, 5).

Calcium kinetics in various disorders have been studied with strontium and calcium isotopes. Assuming a single-compartment system, all but one (RF) of the values reported here for the miscible calcium pool were within normal limits (60 to 110 mg per kg). Normal miscible calcium-pool sizes have been reported by Heaney and Whedon (15) in subjects with a variety of disease processes including idiopathic osteoporosis and rheumatoid arthritis with osteoporosis, and by Bauer, Carlsson, and Lindquist (16) in subjects with leukemia and with nonpituitary brain tumors. The “bone-formation rates” in our patients varied from 5.7 to 11.8 mg per kg per day, with most values within the normal limits given by Heaney and Whedon (8 to 11 mg per kg per day). The calcium kinetics in our study are difficult to compare quantitatively with many other reported studies, since the experimental models and meth-

ods of calculation vary. At present, there is no consensus among investigators in the field regarding a satisfactory mathematical model with which the rates of bone formation and destruction can be accurately measured.

SUMMARY

The present report describes the results of combined metabolic-balance and Ca^{47} -tracer studies in six normocalcemic, ambulatory patients with multiple myeloma. All patients were found to be in significantly negative calcium balance, but no consistent deviations in phosphorus or nitrogen balance were observed. The isotopic studies indicated that endogenous fecal calcium was a very significant route of calcium loss in these patients, exceeding urinary calcium in five of six patients. The results with combined oral and intravenous Ca^{47} -tracer studies strongly suggest that accurate estimates of calcium absorption and endogenous fecal calcium excretion can be obtained with these techniques. The importance of determining the total fecal calcium, as well as of distinguishing unabsorbed dietary calcium and endogenous fecal calcium, is illustrated by the results in one patient before and during 5-fluorouracil therapy.

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