Local and Systemic Effects of Radiation on Bone Metabolism Measured by Quantitative SPECT

Ora Israel, Miguel Gorenberg, Alex Frenkel, Abraham Kuten, Jacqueline Jerushalmi, Gerald M. Kolodny, and Dov Front

Departments of Nuclear Medicine and Oncology, Rambam Medical Center, The Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology School of Medicine and The Rappaport Institute, Haifa, Israel

Quantitative bone scintigraphy (QBS), which measures ^{99m}Tc-MDP uptake expressed as percent of injected dose per cc, indicates bone metabolism. It is measured in the bones of patients before and after radiation treatment and then compared to normal controls. QBS was performed in a group of 22 normal individuals and was measured twice, 2–10 mo (mean 4.9) apart. There was no significant difference between the two measurements. QBS was performed also in 28 patients before, immediately after and at certain time intervals after radiation therapy for cancer. Both the irradiated and the nonirradiated bones showed significant decreases in bone metabolism at 2–18 mo (mean 8.8) after irradiation. In addition, increases and decreases of ^{99m}Tc-MDP uptake were similar in the irradiated and in the nonirradiated bones, and there were significant correlations of the QBS values in the different bones of each individual patient. The etiology of the changes in bone metabolism in the nonirradiated bones is not yet fully understood, but it appears to be the result of a systemic effect of radiation.

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Bone uptake of ^{99m}Tc-MDP can be measured quantitatively using SPECT (*1–3*) and is an indicator of bone metabolism (4,5). We were interested in determining if the technique is sensitive enough to document changes in bone uptake after interventions which cause changes in bone metabolism. Local irradiation of bone is one such intervention. We have therefore measured ^{99m}Tc-MDP uptake in the bones of patients before and after irradiation. It was found that the technique could document quantitatively the known (*6*) decrease in uptake after irradiation of bone. However, our protocol of QBS measurements also included bones which were not irradiated, and when these were measured the nonirradiated bones showed the same changes in uptake of ^{99m}Tc-MDP as the irradiated ones. Initially this was considered to be an artifact, but the phenomenon persisted when more patients were examined. This was in contrast to the high precision observed when we measured QBS in normal controls. We therefore decided to measure bone metabolism prospectively in 28 oncological patients who received radiotherapy and compare these patients with a group of 22 normal controls.

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For reprints contact: Dov Front, MD, PhD, Department of Nuclear Medicine, Rambam Medical Center, Haifa 35254, Israel.

MATERIALS AND METHODS

Quantitative Bone Scintigraphy

Quantitative scintigraphy has been described in detail (*1–3,7*) and will be discussed here only briefly. Quantitative bone scintigraphy was measured using the same methodology as in previous studies (*1,2*). The patient was injected with 20–25 mCi of ^{99m}Tc-MDP and SPECT was performed after 2–4 hr. The amount of ^{99m}Tc-MDP was corrected for decay from the time of preparation to the time the study was actually performed. A complete rotation of 360 degrees, 120 projections (3 degrees apart), with a study time of 20 min was used. For each study 6×10^6 counts were acquired. Raw data were reconstructed using filtered backprojection with a Hanning filter with a cutoff point of 0.5 cycle/cm. Data were analyzed and stored on an Elscint SP-1 computer with an optical disk. This 32-bit computer utilizes our program (*3*) for quantitative calculations. After reconstruction, each image was sectioned at 1-pixel (0.68 cm) intervals in the transaxial, coronal and sagittal planes using a 64×64 byte matrix. For concentration measurements, calculations were performed on the reconstructed data using the threshold method. A threshold of 43%, which was found to give the smallest error in a wide range of phantom studies, was used to measure the concentration of ^{99m}Tc-MDP in the bone (*1–3*). This threshold is suitable for the range of ^{99m}Tc-MDP concentrations encountered in the present study. Counts/voxel were converted to concentration units (μCi/cc), and the percent of injected dose per cc (%ID/cc) was calculated using the identity line of counts/voxel and μCi/cc. The percent of injected dose of ^{99m}Tc-MDP per cc of bone tissue is defined as the QBS value. There is a very good correlation when SPECT-measured concentrations in patients' bones were compared with in vitro measurements in the same bones obtained during surgery (*1*). SPECT measurements of the ilium, sacroiliac region, the lumbar and thoracic spine and femoral shaft were performed.

Patients

Quantitative bone scintigraphy values were measured twice in a group of 22 normal controls at an average interval of 4.9 mo (2–10 mo) (Table 1) in order to determine if there were differences in uptake of ^{99m}Tc-MDP in normals when measured at different times.

TABLE 1
Significance of Difference of QBS Values Between First and Second Study in 22 Controls

Patient no.	Study	Iliac	Sacroiliac	Thoracic vertebrae	Lumbar vertebrae	Femoral shaft
1	First	8.00	11.0	4.24	7.00	4.10
	Second	7.20	9.70	6.06	6.20	3.90
2	First	2.80	2.50	4.33	2.00	1.10
	Second	5.00	4.20	4.95	3.10	1.50
3	First	2.70	1.90	4.60	1.10	1.40
	Second	2.90	2.40	5.00	1.60	1.20
4	First	8.00	6.10	3.10	5.40	1.40
	Second	8.50	6.70	3.90	5.20	1.90
5	First	7.40	6.00	5.82	5.20	2.30
	Second	6.20	5.20	4.82	4.60	1.80
6	First	6.10	3.70	6.31	3.40	2.10
	Second	7.90	5.80	5.50	5.40	2.30
7	First	4.70	3.30	n.d.	4.50	1.50
	Second	6.20	4.60		5.10	1.80
8	First	2.50	3.10	n.d.	2.20	2.44
	Second	2.60	2.60		2.10	3.96
9	First	5.50	4.40	n.d.	3.50	2.66
	Second	5.20	4.10		3.40	2.37
10	First	7.79	7.92	n.d.	4.45	1.70
	Second	9.94	8.37		6.37	2.10
11	First	6.98	7.99	n.d.	3.78	1.40
	Second	7.86	7.13		4.97	1.60
12	First	4.60	5.20	n.d.	3.90	3.18
	Second	5.20	5.10		4.30	2.53
13	First	3.20	3.30	n.d.	2.50	2.53
	Second	4.00	3.90		3.00	2.50
14	First	5.46	5.14	n.d.	4.01	1.93
	Second	5.37	4.01		2.84	2.00
15	First	6.31	6.09	n.d.	4.81	2.00
	Second	5.52	4.71		3.93	2.90
16	First	6.00	6.60	n.d.	5.50	1.28
	Second	6.10	5.50		5.50	1.70
17	First	3.60	3.20	n.d.	2.43	2.40
	Second	4.10	3.30		2.48	2.20
18	First	4.40	6.40	n.d.	5.30	3.17
	Second	4.40	5.70		4.70	3.30
19	First	7.75	5.39	n.d.	6.54	2.80
	Second	7.20	4.90		6.30	3.20
20	First	5.40	3.70	n.d.	4.46	1.40
	Second	5.50	4.44		4.70	1.42
21	First	1.80	1.70	n.d.	1.19	1.58
	Second	1.72	2.61		1.41	2.24
22	First	5.64	3.11	n.d.	3.74	n.d.
	Second	6.40	3.33		4.35	
		p = ns	p = ns	p = ns	p = ns	p = ns

n.d. = not done and ns = not significant.

Twenty-eight patients who received radiation were investigated and diagnosis and treatment are summarized in Table 2. Patients were in clinically stable condition during the study. None of the patients had metastatic disease; they were all in a good general state and were normally mobile. Radiation fields and amounts differed in different tumors according to the routine oncological protocols. Ten patients also received chemotherapy; four, hormonal therapy and two, steroid treatment. There were 16 men and 12 women, aged 34 to 81 yr (mean 63 yr). Follow-up ranged between 2 and 18 mo (mean 8.8 mo), during which SPECT measurements were performed two to five times in each patient. There was no involvement by metastatic disease in any of the bones at the time of the study period. Calcium, phosphorus, alkaline phosphatase and parathyroid hormone (PTH) in the serum were measured before each QBS study in the 13 patients. The QBS values of the ilium, sacroiliac region, lumbar and thoracic spine and femoral shaft before irradiation were compared with the values in the same patient obtained after irradiation using a paired Student's t-test (Table 3). Changes were considered significant if they were beyond the 95% limit of confidence found in the normals for each bone. The relationship of ^{99m}Tc-MDP uptake in irradiated and nonirradiated bones, when each bone

TABLE 2
Diagnosis and Radiation Treatment in 28 Patients Evaluated for Bone Metabolism After Treatment

Patient no.	Age	Sex	Diagnosis	Irradiated region	Irradiated bones	Dose	Other treat.	Study length (mo)	No of stds.
1	70	M	Bladder CA.	Pelvis	Sacroiliac Sacrum Pubis, Ischium	63 GY	Chem.	7	3
2	72	M	Sigmoid CA.	Pelvis Lumbar Verteb.	Lumbar Verteb. Sacroiliac Sacrum	46 GY	—	11	5
3	82	M	Colon CA.	Pelvis	Sacroiliac Sacrum Pubis, Ischium	42 GY	—	4	2
4	69	F	Lung CA.	Upper mediast.	Thoracic Verteb.	40 GY	Hormon. therapy Ster.	4	2
5	68	M	Bladder CA.	Pelvis	Sacroiliac Sacrum Pubis, Ischium	66 GY	—	8	4
6	74	M	Prostate CA.	Prostatic Boost	Sacroiliac Sacrum Pubis, Ischium	66 GY	Hormon. therapy	11	4
7	59	M	Bladder CA.	Pelvis	Sacroiliac Sacrum Pubis, Ischium	63 GY	Chem.	9	4
8	64	F	Caecum CA.	Caecal Fossa	Lumbar Verteb. Iliac Sacroiliac	45 GY	—	5	3
9	79	M	Prostate CA.	Prostatic Boost	Sacroiliac Sacrum Pubis, Ischium	46 GY	—	5	3
10	55	F	Gastric Lymphoma	Upper abdomen	Thoracic Verteb. Lumbar Verteb.	50 GY	Chem.	6	3
11	60	F	Bladder CA.	Pelvis	Sacroiliac Sacrum Pubis, Ischium	50 GY	—	2	2
12	72	F	Ovary CA.	Lumbar Verteb.	Lumbar Verteb.	50 GY	—	9	4
13	46	F	Hodgkin Lymphoma	Mantle	Thoracic Verteb.	30 GY	Chem.	15	4
14	56	M	Bladder CA.	Pelvis	Sacroiliac Sacrum Pubis, Ischium	65 GY	Chem.	10	4
15	35	F	Lymphoma	Mantle	Thoracic verteb.	25 GY	Chem.	12	5
16	63	M	Hypernephroma	Renal Fossa	Lumbar verteb.	45 GY	Hormon. therapy	8	5
17	81	M	Prostate CA.	Prostatic boost	Lumbar verteb. Sacroiliac Sacrum Pubis, Ischium	66 GY	—	14	4
18	65	F	Sigmoid CA.	Pelvis	Lumbar verteb. Sacroiliac Sacrum Pubis	46 GY	—	14	5
19	60	M	Hypernephroma	Renal Fossa	Lumbar verteb. Thorac. verteb.	44 GY	—	11	4
20	62	F	Stomach CA.	Upper abdomen	Thorac. verteb. Lumbar verteb.	50 GY	—	6	2

TABLE 2—*continued*

Patient no.	Age	Sex	Diagnosis	Irradiated region	Irradiated bones	Dose	Other treat.	Study length (mo)	No of stds.
21	64	F	Ovary CA.	Lumbar Verteb. Pelvis	Lumbar verteb. Iliac Sacroiliac Sacrum	30 GY	Chem.	12	5
22	58	M	Lymphoma	Upper abdomen	Thorac. verteb. Lumbar verteb.	15 GY	Chem.	11	5
23	62	M	Hodgkin Lymphoma	Mantle	Thorac. verteb.	36 GY	Chem.	6	3
24	42	F	Endometrium CA.	Pelvis	Sacroiliac Sacrum Pubis, Ischium	46 GY	Chem.	7	4
25	43	M	Hypernephroma	Renal Fossa	Lumbar Verteb.	50 GY	—	6	4
26	64	F	Endometrium CA.	Pelvis	Lumbar verteb. Sacroiliac Sacrum Pubis, Ischium	50 GY	—	11	5
27	58	M	Prostate CA.	Prostatic Boost	Lumbar verteb. Sacroiliac Sacrum Pubis, Ischium	50 GY	—	5	5
28	81	M	Prostate CA.	Prostatic Boost	Sacrum Pubis Ischium	43 GY	Hormon. therapy Ster.	18	3

Hormon. therapy = hormonal therapy; Ster. = steroid therapy and Chem. = chemotherapy.

was compared to all other bones examined in that patient, was calculated using the coefficient of correlation (r) (Table 4).

RESULTS

There was no significant change in the percent of injected dose of ^{99m}Tc MDP uptake (QBS values) in the group of 22 normal individuals in the ilium, sacroiliac region, lumbar and thoracic vertebrae and femoral shaft between the first and the second QBS study (Table 1). The clinical findings of the patients investigated are shown in Table 2. The QBS values in patients both before and after radiation are shown in Table 3. There was a significant difference in each of the bones, other than the femur, between the QBS values obtained before and after radiation both in the irradiated ($p < 0.001$) and in the nonirradiated bones ($p < 0.001$). Twelve patients (nos. 3, 4, 6, 8, 10, 15, 17, 19, 23, 24, 27, 28 in Table 3) showed an increase in bone metabolism in some irradiated and nonirradiated bones. In contrast to the other bones, no significant changes in the measurements of the femoral shaft were seen after irradiation. There was a significant correlation when the QBS values of the iliac bone, sacroiliac region, thoracic and lumbar vertebrae were compared to each other at various intervals after radiation in 23 of 28 patients (Table 4, Fig. 1). Again there was no such correlation when the femoral shaft was compared to the other bones. There were no significant changes in the serum values of calcium, phosphorous, alkaline phosphatase or PTH in any of the 13 patients where these parameters were measured; therefore measurements were discontinued afterwards.

DISCUSSION

The metabolic response of bone to radiation, as measured by QBS was, in general, a decrease of bone metabolism after radiation. In some patients (Fig. 1), there was an early period of increased metabolism after irradiation. However, following this early period there was a significant decrease compared to bone metabolism before irradiation (Table 3). This decrease was more pronounced in the bones which received irradiation than in the nonirradiated bones but there was still a significant decrease in the nonirradiated bones. The decrease in metabolism was not observed in the femoral shaft. The femoral shaft is composed of a large amount of cortical bone which is less active metabolically whereas the other bones are mainly trabecular. Another result of this study is that the pattern of response at different times after the beginning of irradiation was similar in the bones of the same patient (Table 4, Fig. 1). Again, the femur did not correspond to the behav-

TABLE 3

QBS Values (%ID of ^{99m}Tc-MDP per Cubic Centimeter of Bone Tissue) Before and After Radiation

Patient no.	Study	Iliac	Sacroiliac	Thoracic vertebrae	Lumbar vertebrae	Femoral shaft
1	Bef Rad.	7.0	6.3*	8.7	6.1	2.4
	Aft Rad.	6.1	4.4*	6.1	4.6	3.4
2	Bef Rad.	6.6	5.6*	6.0	5.2*	5.3
	Aft Rad.	3.0	2.0*	3.2	2.2*	1.7
3	Bef Rad.	4.7	4.9*	7.9	4.0	2.0
	Aft Rad.	6.4	4.8*	7.3	4.3	3.1
4	Bef Rad.	4.1	3.5	5.0*	3.5	2.0
	Aft Rad.	5.5	4.7	4.1*	4.3	2.1
5	Bef Rad.	3.2	3.4*	4.7	3.6	2.1
	Aft Rad.	2.2	2.5*	4.0	2.9	1.5
6	Bef Rad.	4.9	4.0*	4.6	5.0	1.6
	Aft Rad.	5.4	3.7*	5.8	6.1	2.6
7	Bef Rad.	5.0	6.2*	9.1	7.6	2.7
	Aft Rad.	3.1	3.9*	5.6	4.2	1.5
8	Bef Rad.	5.3*	4.1*	5.7	4.2*	2.2
	Aft Rad.	3.9*	4.0*	5.8	3.0*	2.0
9	Bef Rad.	8.9	7.8*	11.1	10.8	2.5
	Aft Rad.	4.1	3.8*	6.1	5.7	1.7
10	Bef Rad.	5.5	5.2	5.3*	5.2*	2.1
	Aft Rad.	5.5	4.1	5.5*	5.0*	2.4
11	Bef Rad.	6.3	4.9*	n.d.	3.5	2.2
	Aft Rad.	3.9	3.2*	n.d.	2.9	2.0
12	Bef Rad.	3.6	3.8	5.4	6.5*	2.5
	Aft Rad.	2.8	2.8	4.5	3.1*	2.6
13	Bef Rad.	4.9	4.4	5.3*	3.3	1.5
	Aft Rad.	3.0	4.0	2.6*	2.5	2.6
14	Bef Rad.	4.7	4.1*	5.1	4.2	1.9
	Aft Rad.	3.0	2.3*	3.4	2.5	1.5
15	Bef Rad.	3.3	2.6	3.3*	2.5	1.4
	Aft Rad.	3.0	2.8	5.9*	3.2	1.7
16	Bef Rad.	8.5	6.7	7.7	6.4*	2.5
	Aft Rad.	6.1	3.9	5.5	3.9*	2.0
17	Bef Rad.	6.5	5.3*	5.1	4.5*	2.2
	Aft Rad.	7.2	5.2*	6.4	4.7*	2.5
18	Bef Rad.	7.9	7.7*	8.6	6.9*	2.9
	Aft Rad.	4.3	3.7*	5.6	4.2*	2.5
19	Bef Rad.	4.6	3.5	4.5*	3.3*	2.2
	Aft Rad.	4.3	5.1	6.2*	4.5*	2.8
20	Bef Rad.	6.4	6.4	7.0*	6.0*	2.5
	Aft Rad.	5.8	5.7	6.4*	5.5*	2.2
21	Bef Rad.	6.0*	5.1*	6.2	6.2*	4.4
	Aft Rad.	4.1*	3.6*	4.6	4.5*	2.7
22	Bef Rad.	7.1	6.4	4.6*	4.2*	4.0
	Aft Rad.	3.6	3.2	2.7*	2.7*	2.4
23	Bef Rad.	3.4	2.9	2.8*	2.9	1.5
	Aft Rad.	4.2	4.4	3.2*	3.4	1.7
24	Bef Rad.	7.4	6.4*	8.2	7.1	2.2
	Aft Rad.	5.6	4.6*	9.5	5.8	2.0
25	Bef Rad.	n.d.	n.d.	6.5	5.9*	n.d.
	Aft Rad.	n.d.	n.d.	6.2	3.9*	n.d.
26	Bef Rad.	7.4	6.4*	8.0	7.0*	4.8
	Aft Rad.	4.3	3.4*	6.3	3.7*	3.4
27	Bef Rad.	5.0	4.7*	4.9	3.7*	1.3
	Aft Rad.	5.8	4.3*	6.1	4.3*	1.9
28	Bef Rad.	3.6	3.9	3.6	2.6	3.7
	Aft Rad.	4.9	5.6	5.9	3.7	2.4
Paired t-test		Irradiated bones ($n = 41$, $p < 0.001$) Nonirradiated bones ($n = 96$, $p < 0.001$)				

* Irradiated bone.

Bef Rad. = before radiotherapy; Aft Rad. = after radiotherapy end of study period; and n.d. = not done.

TABLE 4

Correlation (r) of QBS Values (%ID of ^{99m}Tc-MDP per Cubic Centimeter of Bone) of Different Bones After Irradiation

Patient no.	Iliac/SI	Iliac/Tho.V	Iliac/Lum.V	SI/Tho.V	SI/Lum.V	Lum.V/Tho.V	Mean
1	0.97	0.90	0.91	0.98	0.98	0.99	0.96
2	0.94	0.98	0.95	0.98	0.99	0.98	0.97
5	0.89	0.48	0.92	0.40	0.75	0.75	0.70
6	0.88	0.77	0.72	0.66	0.46	0.94	0.74
7	0.93	0.80	0.87	0.89	0.93	0.95	0.90
8	0.55	0.21	0.55	0.98	−0.38	−0.69	0.19
9	0.95	0.70	0.66	0.87	0.74	0.87	0.80
10	0.56	−0.96	0.94	−0.77	0.80	−0.99	0.07
12	0.99	0.98	0.77	0.96	0.81	0.64	0.85
13	0.81	0.97	0.89	0.66	0.82	0.87	0.82
14	0.95	0.84	0.91	0.91	0.91	0.94	0.91
15	0.88	−0.04	0.60	0.19	0.76	0.30	0.49
16	0.98	n.d.	n.d.	n.d.	n.d.	0.94	0.96
17	0.73	n.d.	n.d.	n.d.	n.d.	0.70	0.72
18	0.87	0.92	0.97	0.88	0.87	0.95	0.91
19	0.99	0.99	0.98	0.99	0.99	0.99	0.99
21	0.78	0.95	0.99	n.d.	n.d.	0.96	0.92
22	0.99	0.87	0.96	0.84	0.97	0.90	0.92
23	0.91	0.82	0.97	0.98	0.74	0.87	0.78
24	0.81	0.14	0.70	−0.29	0.78	0.20	0.40
25	n.d.	n.d.	n.d.	n.d.	n.d.	0.79	0.79
26	0.98	0.97	0.98	0.92	0.94	0.97	0.96
27	0.68	0.99	0.99	0.67	0.70	0.99	0.84
28	0.76	0.93	0.07	0.72	−0.07	0.36	0.17

SI = sacroiliac; Tho.V = thoracic vertebrae; Lum.V = lumbar vertebrae; and n.d. = not done.

ior of the other bones. These findings appear to indicate that irradiation has a systemic effect since the nonirradiated as well as the irradiated bone responds to radiation in a uniform manner.

There is evidence for changes in bone metabolism in nonirradiated bones in models of irradiated animals. These changes, similar to our findings in humans were discovered accidentally and could not be explained. King (*6*) reported

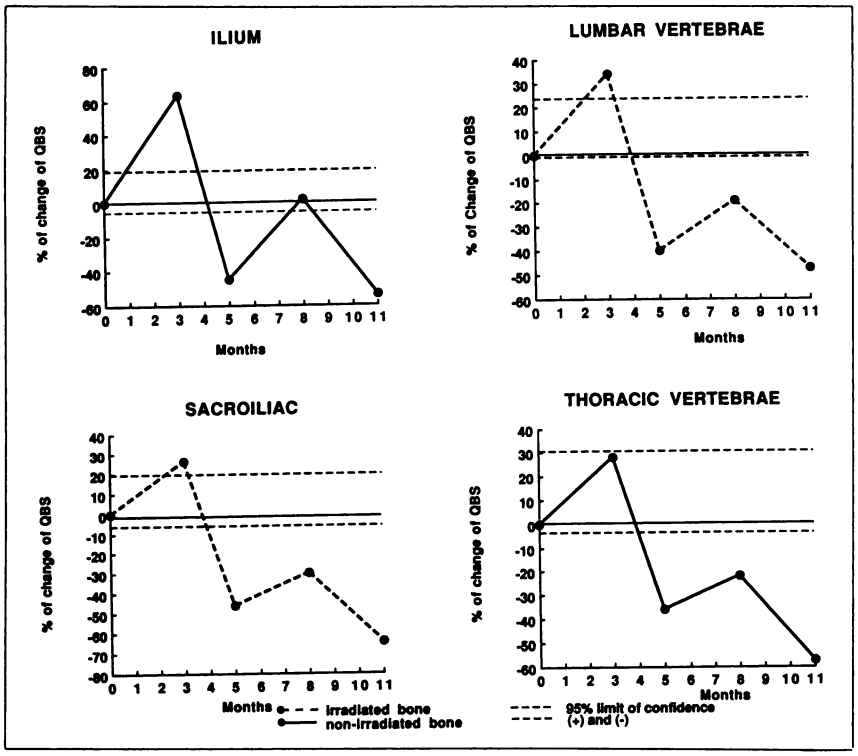

FIGURE 1. QBS values in a patient (no. 2, Tables 2 and 3) irradiated over 3 mo for carcinoma of the sigmoid colon.

radiation changes in the trabecular bone of the contralateral nonirradiated leg in rabbits. He found that there were marked changes in the remodeling of the contralateral nonirradiated leg of rabbits when compared at different times after radiation with the values for rabbits which were not irradiated at all. The histological changes in the nonirradiated bone in rabbits were documented in his publication. It is interesting that King found changes in the trabecular bone and this is similar to our finding of changes in nonirradiated trabecular bone. Effects of irradiation on nonirradiated bone was also observed by Babicky and Kolar who measured the effect of radiation on ^{45}Ca uptake in the bones of mice (*8*).

There is very little in our findings to suggest the cause for these changes. There were no significant changes in calcium, phosphorus, alkaline phosphatase and PTH values in the serum of the patients who were evaluated at the same time when the QBS values were obtained. The effect of radiation on nonirradiated bone appears to be due to a systemic factor, perhaps released into the circulation from the irradiated tissue. However, there is no direct evidence as yet to indicate the existence of such a factor. An indirect mechanism could be postulated in which tissue factors released by irradiation affect the secretion of PTH or calcitonin. PTH, however, was normal in our patients.

The results of the present study might explain abnormalities seen in children who have received radiation. Silber et al. (*9*) describe "other systemic effects" of irradiation of children which cause stature loss. These effects cannot be predicted or assessed accurately in irradiated patients by consideration of only the local effect on the irradiated bones. Decrease in bone turnover in nonirradiated bone may explain stature loss in such children which cannot be explained by local irradiation. If a factor which causes a generalized decrease in bone metabolism does appear after irradiation, it might provide a potential treatment of bone loss in diseases with high bone metabolism such as chronic kidney failure or primary hyperparathyroidism.

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EDITORIAL

Does Radiotherapy Affect Regional Bone Formation?

In this issue of the *Journal*, Israel et al. report a most unusual and surprising finding, namely a marked decrease in ^{99m}Tc-MDP uptake in both radiated and unirradiated bones of cancer patients receiving radiotherapy, and they postulate the possibility of a "systemic factor perhaps released into the circulation from irradiated tissues" as a possible etiology for the phenomenon (*1*). Several questions immediately arise, including these: are the findings real?; if so, what could be the explanation?; and could this be a clue to the long-sought abscopal (remote) effects of radiation?

First of all, it is important to review some basics. Technetium-99m-MDP uptake clearly measures not just "bone metabolism" as suggested by Israel et al., but new bone formation, as shown by many investigators (*2–6*) and by computer modeling (*7*), and similar to the uptake of mineral skeletal tracers (*2,5,8,9*). Mathematical modeling of ^{99m}Tc-MDP kinetics allows us a unique opportunity to determine the effects of perturbations on the system. Multiple causes can be seen to affect bone uptake adversely: increased urinary excretion of tracer; decreased cardiac output; expansion of ECF space; decreased tracer uptake by forming bone; and selectively decreased bone blood flow (*9*). However, there is no consistent clinical pattern or other evidence provided by Israel et al. to suggest that any of these potential explanations is valid.

With respect to the reality of the findings, a review of the literature demonstrates few instances of a distant depressive effect of radiotherapy on nonirradiated bones. King et al. found a decrease in bone formation as measured by tetracycline labeling in the contra-lateral (nonirradiated) hind leg of irradiated rabbits, and they were at a loss to explain the findings (*10*). On the other hand, Babicky and Kolar studied the long-term effects of acute irradiation of 20 Gy in mice but found no decrease in Ca-45 uptake in the contralateral leg, with frequent de-

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For reprints contact: N. David Charkes, MD, Nuclear Medicine/Diagnostic Imaging, Temple University Hospital, 3401 N. Broad St., Philadelphia, PA 19140.