Administered Dose and Tumor Dose of Bleomycin Labeled with Cobalt-57 in Mice and Men

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Tumor concentrations of the chemotherapeutic drug, bleomycin, labeled with cobalt-57 (Co-bleo) were compared in mouse tumor models and in human lung tumors using quantitative single-photon emission computed tomography. Drug concentrations in histologically similar human tumors showed marked variability for the same injected dose (ID). Small cell carcinomas showed concentrations between 1.09 and 8.85 %ID/cc $\times 10^{-3}$ while non-small cell lung tumors showed a concentration variation between 0.36 and 6.75 %ID/cc $\times 10^{-3}$. In contrast to the situation in human tumors, uptake in mouse tumors showed only slight variability in animals with the same tumor model. EMT-6 tumors in mice showed at 6 hr significantly higher uptake of Co-bleo ($p < 0.001$) and significantly higher tumor-to-lung ratio ($p < 0.001$) when compared to murine fibrosarcomas. The EMT-6 tumors in contrast to the fibrosarcomas responded to bleomycin treatment in a dose dependent manner. The results indicate that while in mice the tumor dose closely follows the administered dose, in humans, the tumor dose and the tumor-to-lung ratio in the individual patient cannot be predicted from the administered dose.

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Drug-sensitive tumors can only be affected by the fraction of a chemotherapeutic drug which is delivered to them by their blood supply. The goal of cancer chemotherapy is to deliver the highest possible amount of drug to the target tissue—the tumor—while causing minimal possible toxicity to normal sensitive tissues (*1*). In human solid tumors, however, there is little data about the "tumor dose"—the fraction of the administered dose of a chemotherapeutic drug which is actually delivered to a tumor. It is assumed that in patients there is a direct relationship between the administered dose and the tumor dose, i.e., that the administration of a high dose will result in a high tumor dose in each patient and vice versa. There is also little information in humans about the fraction of the administered dose that is delivered to sensitive organs. Most of the data on pharmacokinetics and distribution of chemotherapeutic drugs is derived from preclinical studies in tumor models in animals (*2,3*).

In the study reported here, cobalt-labeled bleomycin (Co-bleo) was used as an example of the disposition of a chemotherapeutic drug in animal tumor models which respond and do not respond to treatment. The uptake in these animal tumor models was compared with the information obtained from the concentration of Co-bleo in human tumors in vivo using quantitative single-photon emission computed tomography (SPECT). We also used quantitative SPECT to measure the in vivo concentration of Co-bleo in patients' lungs, which are a major site of bleomycin-induced toxicity, in order to determine the tumor-to-lung ratio of the drug.

MATERIALS AND METHODS

Mice Studies

Two experimental murine tumors were used to determine the relationship between the administered dose and tumor dose, EMT-6 sarcoma and a methylcholantrene-induced fibrosarcoma. The EMT-6 tumor grows in Balb/C mice, the fibrosarcoma grows in C57 black mice.

EMT-6 sarcoma cells (kindly provided by Dr. B. Teicher, Dana Farber Cancer Institute, Boston, MA) were grown in vitro, 1×10^6 cells were injected subcutaneously into the thigh of 10–12-wk-old female Balb/C mice weighing 19–21 g. Methylcholantrene-induced fibrosarcoma is maintained in our laboratory by serial subcutaneous transplantations of $\sim 10^6$ cells also into the thighs of 6-wk-old female C57 black mice weighing 19–21 g. The same bleomycin (Blenoxin, Lundbeck, Copenhagen, Denmark) labeled with cobalt-57 (^{57}Co) (Du Pont, N. Billerica, MA) used for human studies was used in mice. Five microcuries were injected into the intraperitoneal space 7–10 days after the inoculation of the EMT-6 sarcoma and

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after transplantation of the fibrosarcoma. Sixty-six Balb/C and 30 C57 black mice were used for measurement of tumor and lung concentrations of the drug. Activity was measured in a gamma well counter (Atomic Product Corp., New York) and results were expressed as percent of administered dose per gram tissue (%ID/g). Thirty-four mice were evaluated for treatment. Growth curves were obtained for untreated controls and before and after treatment with a single dose of 30 mg/kg or 45 mg/kg of bleomycin.

Human Studies

Thirty-two patients were investigated. The concentration of Co-bleo was measured in 12 small cell lung carcinomas and in 20 non-small cell lung carcinoma. All patients were newly diagnosed and the studies were performed before any treatment was initiated. Co-bleo concentration was also measured using SPECT in 20 normal lungs of patients with non-small cell lung carcinomas. The purpose of the study was explained and an informed consent approved by our institution was obtained from each of the patients.

The relationship between the dose of the intravenously injected drug and the dose found in the tumor was studied using the quantitative SPECT technique described previously (*4–6*). The studies were performed using a digital gamma camera with a rotating gantry (Apex, ECT-415, Elscint, Haifa, Israel). A 64 × 64 byte matrix was used and 2,500–4,000 counts were collected for each projection. Sixty projections six degrees apart were acquired and $1.5–2.4 \times 10^5$ counts were accumulated for the entire study. For reconstruction and data processing a 32-bit computer (SP-1, Elscint, Haifa, Israel) was used. Using a Hanning filter, the data were reconstructed by backprojection in the transaxial, sagittal, and coronal planes. Attenuation and Compton scatter correction were not performed. Quantitation was performed using the fixed threshold method. A threshold of 0.43 (43% of the maximal counts in a slice) was used to define the tumor. For each slice, the pixels containing counts that exceeded that of the threshold were used to calculate the volume and concentration in the tumor. This threshold was experimentally found to give the best correlation between measured and real volumes and concentrations in a large series of phantoms using technetium-99m (^{99m}Tc) and ^{57}Co. This method was previously validated by the in vitro/in vivo correlation of SPECT concentration measurements of ^{99m}Tc-glucoheptonate and the actual concentration in samples of tumors obtained at surgery. The collected data were stored on an optical disk (Elscint, Haifa, Israel).

Two milligrams of bleomycin used for routine chemotherapy were labeled with two millicuries of ^{57}Co-57 in our laboratory as previously described (*7,8*) and were injected intravenously. Drug concentration in vivo was measured by SPECT as percent of injected dose per cubic centimeter (%ID/cc) of tumor. The concentration of Co-bleo was measured at different times after the intravenous injection.

The integral of the concentration in the tumor between 30 min and 8 hr was defined as the tumor cumulative concentration (TCC) and was calculated using the formula:

$$TCC = \int_{30'}^{480'} C_T(t)\, dt,$$

where C_T represents the concentration in the tumor.

In 20 patients with non-small cell lung carcinoma, in addition to the measurement of Co-bleo concentration of the radiopharmaceutical in normal lung tissue the lung cumulative concentration (LCC) was calculated using the formula:

$$LCC = \int_{30'}^{480'} C_L(t)\, dt,$$

where C_L represents the concentration in the lung.

The tumor-to-lung ratio was defined as the ratio of the concentration in the tumor to the concentration in the normal lung. It was calculated at different time points—30 min, 120, 240, and 480 min as:

$$\text{Tumor-to-lung ratio} = \frac{C_T(t_i)}{C_L(t_i)},$$

where t_i = 30 min, 120, 240, and 480 min and for the whole period of the study as:

$$\text{Tumor-to-lung ratio} = \frac{TCC}{LCC}.$$

The tumor-to-lung ratio does not take into consideration the lower tissue density of the lungs when compared with solid tumors.

RESULTS

Tumor drug concentration over time in murine tumors is shown in Table 1 and Figure 1. Drug concen-

TABLE 1
Concentration of Co-bleo Over Time Expressed as %ID/g in Murine Tumors

	30′	60′	120′	180′	240′	360′
EMT-6	n = 14	n = 11	n = 9	n = 11	n = 9	n = 12
mean	2.27	2.24	2.29	2.26	1.66	1.54
s.d.	0.22	0.30	0.20	0.35	0.31	0.45
Minimal value	2.00	1.44	2.00	1.70	1.05	0.95
Maximal value	2.80	2.70	2.56	2.91	2.06	2.41
Variation coefficient	9.9	13.6	8.9	15.6	18.4	28.9
Fibrosarcoma	n = 6	n = 8	n = 9	—	—	n = 7
mean	2.27	1.37	1.23	—	—	0.56
s.d.	0.47	0.45	0.39	—	—	0.39
Minimal value	1.70	1.01	0.86	—	—	0.08
Maximal value	3.01	2.40	2.20	—	—	1.31
Variation coefficient	20.7	32.5	31.9	—	—	69.4

trations in the EMT-6 sarcomas were higher than that in the fibrosarcomas. The concentration differences among the individual tumors in each group were small in both tumors. Concentrations over time in EMT-6 showed only a small variation. The highest variation was between 0.95 to 2.41 %ID/g at 360 min. Among the fibrosarcomas, there was a steady decrease in concentration with a maximum variation in the range of 0.08–1.31 %ID/g at 360 min.

Concentrations over time in the mouse lungs are shown in Table 2 and Figure 2. The maximum variation in the lung concentration in Balb/C mice bearing EMT-6 tumors ranged between 0.14 and 0.45 %ID/g at 180 min. The maximum differences in concentration of Co-bleo in the lungs of C57 black mice with fibrosarcomas ranged between 0.19 and 0.82 %ID/g at 360 min. The tumor-to-lung ratio for Co-bleo in EMT-6-bearing mice was 1.16–12.15 and 1.07–1.81 for mice with fibrosarcomas. The Co-bleo tumor-to-lung ratio remained essentially constant over time for the fibrosarcoma-bearing mice while it increased in the EMT-6-bearing mice. Uptake of Co-bleo at 360 min in EMT-6 tumors, 1.54 %ID/g, was also significantly higher ($p < 0.001$) than uptake at 360 min in fibrosarcomas, 0.56 %ID/g. The tumor-to-lung ratio in EMT-6- (12.07 at 360 min) containing animals was significantly higher ($p < 0.001$) than in the fibrosarcoma-containing animals (1.37 at 360 min). EMT-6 tumors responded to treatment and the growth curves in controls and treated animals are shown in Figure 3. The fibrosarcomas did not respond to treatment and there was no difference in the growth curve between treated and nontreated tumors.

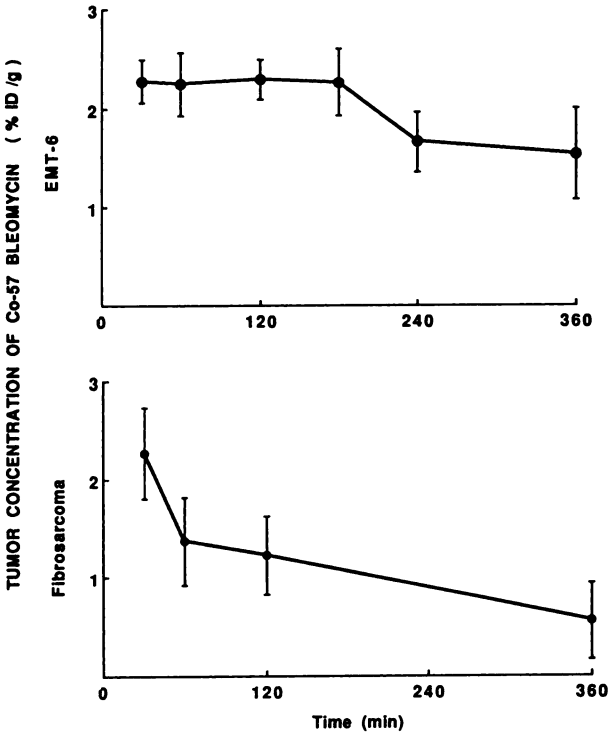

FIGURE 1
Uptake of ^{57}Co-bleomycin expressed as %ID/g (mean ± s.d.) in murine tumors.

TABLE 2
Concentration of Co-bleo Over Time Expressed as %ID/g and Tumor-to-Lung Ratio in Lungs of Balb/C Mice Bearing EMT-6 and C57 Black Mice Bearing Fibrosarcoma

	30′	60′	120′	180′	360′
Lung concentration Balb/C	n = 5	n = 3	—	n = 5	n = 5
mean	2.19	1.23	—	0.21	0.10
s.d.	0.57	0.27	—	0.12	0.03
Minimal value	1.25	0.96	—	0.14	0.06
Maximal value	3.00	1.60	—	0.45	0.14
Variation coefficient	26.1	21.7	—	57.2	30.8
Tumor-to-lung ratio Balb/C EMT-6					
mean	1.16	1.99	—	12.15	12.07
s.d.	0.29	0.45	—	3.70	3.33
Minimal value	0.87	1.35	—	5.64	8.07
Maximal value	1.68	2.37	—	16.00	18.20
Variation coefficient	24.7	22.8	—	30.5	27.6
Lung concentration C57 black	n = 6	n = 8	n = 7	—	n = 6
mean	2.29	1.20	0.67	—	0.47
s.d.	0.55	0.22	0.19	—	0.24
Minimal value	1.29	0.70	0.36	—	0.19
Maximal value	3.20	1.46	0.91	—	0.82
Variation coefficient	37.0	18.4	27.6	—	50.0
Tumor-to-lung ratio C57 black (fibrosarcoma)					
mean	1.07	1.18	1.81	—	1.37
s.d.	0.44	0.42	0.69	—	0.98
Minimal value	0.71	0.78	0.97	—	0.15
Maximal value	2.02	2.14	2.89	—	2.62
Variation coefficient	41.1	35.3	38.2	—	71.6

Concentrations over time of Co-bleo were measured in 32 human tumors. As compared with mouse tumors, differences among individual human tumors were very striking. At each point in time starting 30 min after the i.v. administration of the drug, there were marked differences in the concentration of Co-bleo in each tumor (Table 3, Fig. 3), indicating the marked variation in tumor drug delivery in individual patients harboring histologically similar tumors. Maximum differences in drug concentrations in small cell lung carcinoma were observed at 480 min with a range of concentrations between 1.09 and 8.85 %ID/cc × 10^{-3} with a variation coefficient of 57.3. In 20 patients with a non-small cell lung carcinoma, the maximum variation in drug concentration was found at 480 min with concentrations ranging from 0.36 to 6.75 %ID/cc × 10^{-3} and a variation coefficient of 51.1 (Table 4, Fig. 4).

Such variations were not observed in 20 normal lungs (Table 5, Fig. 5) available for SPECT measurements in

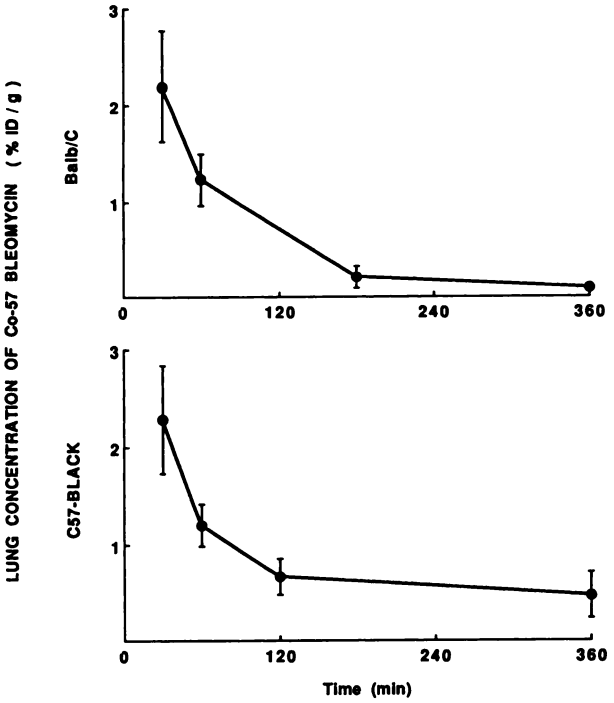

FIGURE 2
Uptake of ^{57}Co-bleomycin expressed as %ID/g (mean ± s.d.) in murine lungs.

patients with non-small cell lung carcinoma. The maximum difference in drug concentrations in the normal lung tissue ranged between 1.73 and 6.53 %ID/cc × 10^{-3} at 30 min. The tumor-to-lung ratio of the cumulative drug concentrations ranged between 1.04 and 2.78 (Table 5).

DISCUSSION

Since it has been difficult to measure the concentration of chemotherapeutic drugs in patients except by surgical biopsy, most information on drug uptake has

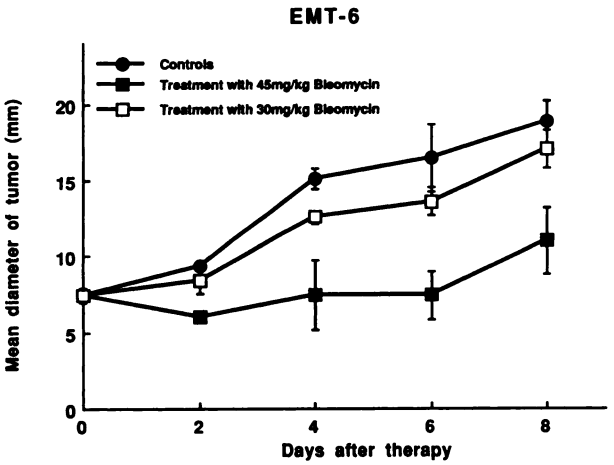

FIGURE 3
Growth curves in EMT-6 tumors before and after bleomycin treatment.

TABLE 3
Concentration (%ID/cc × 10^{-3}) Over Time of Co-bleo and TCC (%ID/cc × min) in 12 Patients with Small Cell Lung Carcinoma

Patient no.	Sex	Age	Concentration over time 30′	120′	240′	480′	TCC
1	M	72	6.39	8.00	9.19	8.85	3.83
2	M	55	4.61	4.04	3.60	3.54	1.71
3	F	60	4.40	2.35	1.92	1.09	0.89
4	M	64	5.84	4.87	4.85	5.09	2.27
5	M	69	4.61	3.76	4.09	2.59	1.59
6	M	65	4.24	2.83	2.25	1.71	1.07
7	M	66	6.30	6.81	6.61	6.94	3.03
8	M	61	4.97	4.08	3.35	2.87	1.60
9	M	50	4.27	3.68	3.36	3.08	1.55
10	M	71	5.34	4.27	2.31	3.24	1.59
11	M	65	4.59	4.00	3.28	2.91	1.55
12	M	75	5.22	3.93	3.17	2.65	1.52
mean			5.06	4.38	4.00	3.71	1.87
s.d.			0.73	1.51	1.98	2.21	0.79
Variation coefficient			14.4	34.3	49.5	57.3	42.8

TABLE 4
Concentration (%ID/cc × 10^{-3}) Over Time of Co-bleo and TCC (%ID/cc × min) in 20 Patients with Non-small Cell Lung Carcinoma*

Patient no.	Sex	Age	Concentration over time 30′	120′	240′	480′	TCC
1	F	57	3.41	2.64	2.17	1.86	1.04
2	M	56	2.77	2.17	1.57	1.31	0.79
3	M	54	3.45	3.52	2.84	2.26	1.31
4	M	66	2.61	1.53	1.24	0.86	0.59
5	M	59	5.47	3.58	2.97	2.30	1.40
6	F	59	3.20	2.40	1.99	1.57	0.94
7	M	63	5.04	3.50	2.85	2.25	0.94
8	M	58	3.70	1.29	0.91	0.36	0.51
9	F	61	3.85	2.64	2.23	1.62	1.02
10	M	73	5.26	3.95	3.59	3.44	1.69
11	M	70	4.97	3.95	2.99	2.35	1.46
12	M	68	3.74	3.24	2.95	2.62	1.34
13	M	55	9.52	6.62	4.10	3.72	2.25
14	M	54	4.15	3.83	3.40	2.78	1.51
15	M	64	5.41	3.47	2.88	2.50	1.40
16	M	62	4.00	3.14	3.00	2.60	1.35
17	M	54	4.54	4.33	4.60	3.49	1.89
18	F	75	5.61	3.86	3.06	2.43	1.49
19	M	65	6.49	6.03	6.66	6.75	2.93
20	M	72	4.16	4.38	3.97	3.20	1.73
mean			4.57	3.50	3.00	2.51	1.38
s.d.			1.51	1.26	1.23	1.28	0.55
Variation coefficient			33.10	35.90	41.20	51.10	39.90

* Patients 1–15 had an adenocarcinoma and Patients 16–20 had a squamous-cell lung carcinoma).

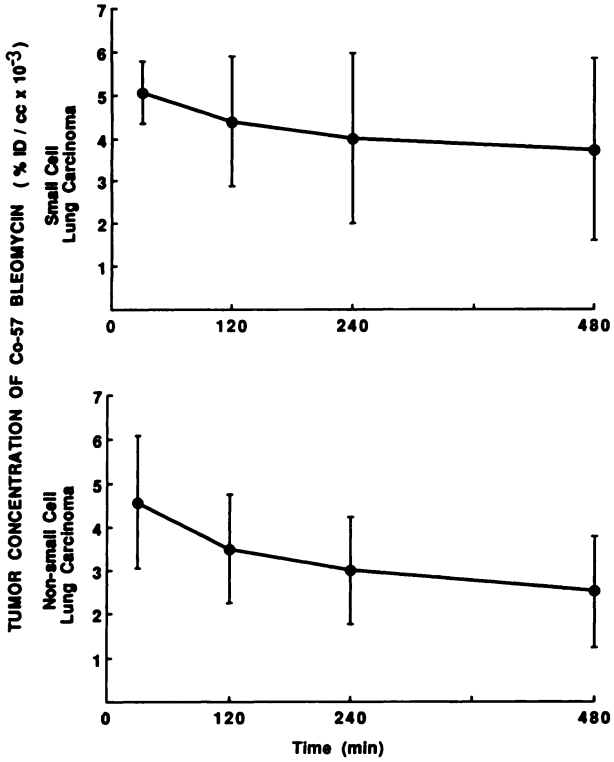

FIGURE 4
Uptake of ^{57}Co-bleomycin expressed as %ID/cc × 10^{-3} (mean ± s.d.) in human tumors.

been derived from preclinical pharmacologic studies in animal tumor models. Quantitative SPECT enables the accurate measurement in vivo of the concentrations of labeled drugs in human tumors (*4–6*). In the present study, the concentration of labeled bleomycin in mouse tumor models was compared to that found in human tumors using SPECT.

Bleomycin was used in this study in humans because it is a chemotherapeutic drug which can be readily labeled without significantly affecting its binding to DNA, the site of its biologic activity (*9*). Co-bleo binds to bleomycin antibody like Cu-bleomycin and copper-free bleomycin suggesting a similar configuration (*10*). Co-bleo is excreted unchanged in the urine (*9*). Co-bleo forms an equimolecular complex which binds to DNA. DNA strand scission by bleomycin is believed to be responsible for its therapeutic effect and requires metal ions as a cofactor. Cobalt- and Fe-bleomycin give a similar DNA breakage pattern and they remain bound to bleomycin intracellularly (*11*). In the present study, we used Co-bleo as an example of the disposition of a labeled chemotherapeutic drug both in murine and human tumors and in the lungs.

The results of this study show that in inbred mice the tumor dose was relatively proportional to the adminstered dose. Essentially the same fraction of the administered dose reached each tumor in different mice. They also show that higher uptake in the tumor and a higher tumor-to-lung uptake correlate with a better response to treatment. These studies in mice also show that the therapeutic response is tumor dose dependent.

In humans, in contrast to the animal studies, for the same administered dose marked variations were found in the tumor dose, even in tumors with the same histology. This appeared to be a common characteristic of all the human tumors studied. Significant variations in the bioavailability of a drug in the blood has been described for orally administered drugs due to variability in absorption (*12,13*). The present study shows that marked differences in drug concentrations in solid tumors should also be recognized in cases of an intravenously administered drug. These differences in tumor concentration have previously not been considered when planning chemotherapy. The question has not been raised probably because preclinical studies in tumor models have not indicated that such critical prob-

TABLE 5
Concentration of Co-bleo (%ID/cc × 10^{-3}) Over Time, Cumulative Concentration (%ID/cc × min), and Tumor-to-Lung Ratio in 20 Patients with Non-small Cell Lung Carcinoma

		30′	120′	240′	480′	Cumulative concentration
Lung	mean	2.92	2.15	1.62	1.16	0.77
	s.d.	1.03	0.75	0.52	0.55	0.22
	Minimal value	1.73	1.00	0.67	0.31	0.40
	Maximal value	6.53	4.05	3.21	2.97	1.49
	Variation coefficient	35.20	35.00	31.70	47.60	28.90
Tumor-to-lung ratio						
	mean	1.61	1.64	1.84	2.28	1.77
	s.d.	0.42	0.36	0.55	0.94	0.44
	Minimal value	1.04	0.95	1.11	0.95	1.04
	Maximal value	2.82	2.39	3.17	5.06	2.78
	Variation coefficient	25.80	22.00	30.00	41.30	24.70

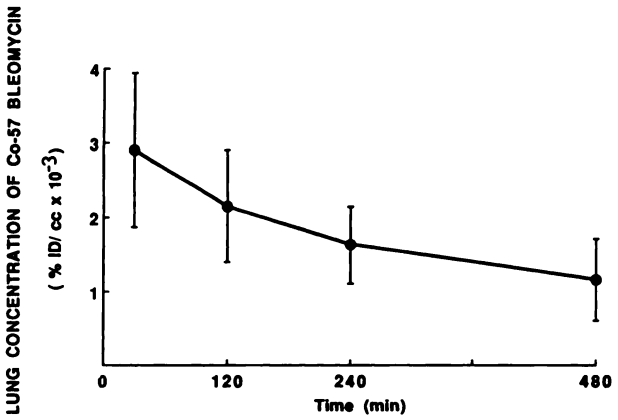

FIGURE 5
Uptake of ^{57}Co-bleomycin expressed as %ID/cc × 10^{-3} (mean ± s.d.) in human normal lung tissue.

lems might arise in humans. Although differences in drug delivery might be suspected, considering human tumor heterogeneity (*14*), patients with different fractions of administered dose delivered to their tumors are usually treated with drug doses without considering the individual variability in tumor drug uptake.

Animal tumors unlike human tumors contain relatively homogenous populations of cells which have been genetically selected by long-term cultivation in tissue culture and animal transplantation. The animals used for these studies have also been bred to be genetically similar. It is not surprising, therefore, that the tumor dose is proportional to the administered dose in each animal. This obviously is not the case in humans. In clinical practice, the usual approach is to give the same protocol dose normalized for body surface to a group of patients with the same tumor histology and then escalate to some toxicity. One assumes that the administration of a dose that produces toxicity just short of dangerous will result in the tumor having an opportunity to obtain as much of the drug as possible. While this appears true for the two animal tumor models we have studied, it appears that in humans some tumors will be exposed to a much lower concentration of the drug than others. The large variations in drug concentration in human tumors as compared with mouse tumors may have not been previously fully appreciated because there has been no method to systematically measure drug concentration in human tumors in vivo.

The tumor-to-lung ratio of Co-bleo was also significantly higher in EMT-6-bearing balb/C mice as compared with C57 black mice bearing fibrosarcomas. This correlated with the therapeutic response. Use of quantitative SPECT enabled us to measure the concentrations of Co-bleo in human lungs and to calculate the tumor-to-lung ratio. The significance of this parameter in humans remains to be investigated.

There are a number of variables (*14*) to be considered when planning chemotherapy. In sensitive tumors, the response is dependent on tumor dose. This study shows that although the relationship between administered dose and tumor dose can be predicted in mice, and response is dependent on tumor dose, it cannot be predicted in individual tumors in humans. Future studies incorporating a large series of patients who will have radionuclide quantitative imaging and who will be treated with bleomycin or other drugs in which labeling does not alter biodistribution will determine the clinical effectiveness of tumor dose measurements. Potentially, nuclear medicine techniques can play an important role in the evaluation of patients before chemotherapy. Measurement of uptake of iodine-131 has been classically used before treatment of thyroid carcinoma to determine if iodine concentration is high enough to achieve a radiation dose which will affect the tumor. The same principle can be applied to chemotherapy of other tumors in the individual patient using quantitative SPECT. If the tumoricidal effect of a drug is dependent on the amount of the drug to which sensitive tumor cells are exposed, then tumor dose, not administered dose, should be among the factors to be considered when planning effective chemotherapy.

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Correlation of Neoplasms with Incidence and Localization of Skeletal Metastases: An Analysis of 1,355 Diphosphonate Bone Scans

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Detection of metastatic disease by bone scintigraphy is presently experiencing a rapid growth in nuclear medicine. Initially, bone scintigraphy was limited to ^{85}Sr, soon followed by a rapid succession of isotopes, including ^{87m}Sr and ^{18}F. Since its introduction in 1971 by Subramanian, ^{99m}Tc-polyphosphate has been responsible for a dramatic increase in the use of the bone scan for the management of patients with malignant metastatic neoplasms and osseous disorders.

Each successive radionuclide bone agent has had both higher sensitivity for detection of metastases and the ability to produce more rapidly higher quality scintigrams than roentgenography. In this report, the incidence and location of metastatic skeletal involvement, as derived from clinical trials with ^{99m}Tc-Sn EHDP, are presented and compared to previous studies of osseous metastatic detection of the most common forms of neoplasm.

During the clinical trials of ^{99m}Tc-Sn EHDP, 1,891 patients from 16 medical institutions were scanned. Patients were scanned an average 3.5 hours after administration of the agent.

Of the total number of patients, 1,355 were scanned for evaluation of metastatic involvement from nonosseous primary malignant neoplasm. The remaining indications were associated with both primary bone neoplasms and nonmalignant diseases and were excluded from this paper. The percentage of abnormal scans for all 1,355 patients with nonosseous primary malignant neoplasms, irrespective of indication, was 60%.

As expected, carcinoma of the breast (28%), lung (16%), and prostate (14%) constituted the major source of all metastatic neoplasms to bone. Except for lymphoma, bladder, and thyroid carcinomas, all the primary indications had 50% or greater incidence of metastatic skeletal involvement.

It is evident from the 60% abnormal scan level and the widespread dissemination through the skeleton that whole-body bone scans should be used in staging all forms of malignant carcinomas that are known to metastasize to bone, as well as in follow-up management of carcinoma patients. ■

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The Use of the Counting Rate Profile in Radioisotope Scanning Techniques

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In the application of the automatic scintillation scanner for the visualization of large organs by means of deposited radioactivity, one of the primary problems is the differentiation of small variations in counting rate between the site of interest and its surrounding environment. For this reason, attempts have been made to accentuate such differences by means of non-linear recording devices. These systems have fallen into two forms: those utilizing a counting rate cut-off circuit in which the printing mechanism is only activated over areas exceeding a preselected rate; and those utilizing the logarithmic response of film density to light.

The disadvantages of these techniques are twofold: in the counting rate controlled technique, no record is obtained from any areas with deposition rates below a set level; and in the light recording methods, the sharp accentuation is likely to reach a density saturation over a short counting range, losing information above and below this range. For these reasons, it has been necessary to accurately measure and record the linear scan or "liver profile" for variations of counting rate during excursions of the detector over the body surface. The profiles are referred to the anatomical landmarks, permitting the evaluation of the size and position of the liver, as well as the changing pattern of activity over different areas referred to the corresponding lines of the dot scan.

In our institution, it is felt that optimum results are obtained by using pre-dot scan survey profiles for accurate setting of the cut-offs and optimum levels and utilizing both the conventional dot scan and serial profiles for interpretation. While the area scan is useful for the general organ outline, the serial profiles recorded at the time of the dot scan allow a more accurate statistical analysis of any given area for differentiation of deviation from homogeneous distribution. Since the multiple juxtaposed profiles contain all the information in a convenient visual form, it is possible that this technique may supplant our present method. ■