OPTIMIZATION OF THE RATIO OF STANNOUS TIN: ETHANE-1-HYDROXY-1, 1-DIPHOSPHONATE FOR BONE SCANNING WITH ^{99m}Tc-PERTECHNETATE

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Using synthetic hydroxyapatite (HA) as an in vitro skeletal model, the optimum formulation of a ^{99m}Tc-distannous ethane-1-hydroxy-1, 1-diphosphonate (^{99m}Tc-Sn·EHDP) bone scanning agent was determined by measurement of the amount of radiotagged components (^{99m}Tc, ^{113}Sn, and 1-^{14}C-EHDP) on HA. A range of EHDP to stannous chloride weight ratios (5:1–50:1) was found to yield complete (>95%) sorption on HA of the ^{99m}Tc-Sn·EHDP bone scanning agent. Using the 12:1 and 50:1 ratios, organ distribution and blood clearance for 1-^{14}C-EHDP, ^{113}Sn, and ^{99m}Tc were determined in Sprague-Dawley rats. Major whole organs, selected skeletal samples, urine, and feces were assayed by liquid scintillation and gamma spectrometers. The ^{99m}Tc-Sn·EHDP agent was found to be nearly evenly distributed between the skeleton and urine with less than 2% of the dose in soft tissue.

The ^{99m}Tc-Sn·EHDP agent yielded excellent scintiscans of the skeletal system. The rapid blood clearance is comparable to ^{18}F, and the physical and chemical properties of the diphosphonate agent suggest an advantage over the ^{99m}Tc-labeled polyphosphate or pyrophosphate bone scanning agents.

Ever since Treadwell's (*1*) work with ^{89}Sr, the basis for selecting many of the radionuclides to use in bone scanning has been the ability of the radioisotopes to exchange with the ions normally found in hydroxy apatite (HA). Thus the most commonly used scanning agents have been ^{85}Sr and ^{18}F. Recently, a chemical sorption approach with polyphosphates coupled to the favorable nuclear properties of ^{99m}Tc has been found to produce good skeletal imaging. The scintigraphs obtained with the ^{99m}Tc-tripolyphosphate (*2*) and ^{99m}Tc-polyphosphate (PP-46) (*3*) are very exciting, but polyphosphates in general have a number of inherent limitations such as distribution of molecular weight and instability in vivo resulting from hydrolysis by endogenous enzymes. Based on our extensive work with various agents which can chemisorb on HA (*4*), it was felt that the use of disodium ethane-1-hydroxy-1, 1-diphosphonate (EHDP™), a compound which is both enzymatically stable and has a definitive molecular weight, should prove to be an excellent bone scanning agent when combined with ^{99m}Tc-pertechnetate (*5,6*) and provide a decided advantage over present bone scanning agents. Subsequent animal (*7–9*) and clinical studies (*10–12*) have confirmed the efficacy of the diphosphonate for bone scanning.

The properties of distannous-ethane-1-hydroxy-1, 1-diphosphonate (Sn·EHDP) were used to produce a very effective bone scanning agent upon addition of ^{99m}Tc-pertechnetate (^{99m}Tc-Sn·EHDP). An optimum ratio of the individual components of the Sn·EHDP complex was determined by experimentation in vitro. The distribution of the optimized, water soluble bone scanning agent was then determined in rats using ^{99m}Tc-, ^{14}C-EHDP, and ^{113}Sn-labeled components. Excellent images of the normal skeleton in rats were obtained with a scintillation camera.

MATERIALS AND METHODS

The components of the skeletal scanning agent are EHDP, stannous chloride, and ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$). The 1-^{14}C-EHDP was prepared by treating phosphorous tetraoxide (P_4O_6) with 1-^{14}C-acetic acid (*13*). Chemical purity of the 1-^{14}C-EHDP acid monohydrate was obtained by repeated recrys-

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tallization from water (99% pure as determined by analysis for minor constituents such as phosphite and water and by NMR, elemental analysis, thin-layer chromatography, and other physical techniques).

The labeled stannous chloride was prepared by the addition and subsequent isotopic exchange of a dilute hydrochloric acid solution of $^{113}SnCl_2$ (New England Nuclear). The $^{99m}TcO_4^-$ was obtained from an oxidant-free commercial generator (New England Nuclear, Squibb Hi-Con). All data were analyzed on Nuclear Data 2200 Series Nuclear Data System with a high-resolution, 30-cc lithium-drifted germanium [Ge(Li)] detector (ORTEC) and Packard Model 3375 beta spectrometer. Scintigraphs were obtained with a Nuclear-Chicago Pho/Gamma HP scintillation camera using a ⅛-in. pinhole and a 140-keV, high-resolution collimator.

Preparation of ^{99m}Tc-Sn·EHDP. The entire labeling procedure, with the exception of weighing the $SnCl_2$ and EHDP, was performed in a high-purity nitrogen atmosphere in a glove bag (Instruments for Research and Technology). A stock solution of tin was prepared by dissolving 10-mg reagent-grade anhydrous $SnCl_2$ flakes (Matheson Chemical) in sterile water and diluting to 100 ml in a volumetric flask. The EHDP (61 mg) as the disodium salt was similarly dissolved and diluted to 20 ml with sterile water. The Sn·EHDP complex was prepared by the quantitative addition of 10 ml of the $SnCl_2$ solution to the entire EHDP solution. For each test vial, the 30 ml of the Sn·EHDP solution was passed through a 0.22-micron Millipore filter into a sterile beaker. From the beaker 3-ml portions were transferred by syringe to serum vials. No pH adjustment is necessary with this aqueous preparation.

The ^{99m}Tc-Sn·EHDP bone scanning complex was then prepared by adding 2 ml of $^{99m}TcO_4^-$ of appropriate activity from the generator to the Sn·EHDP solution. The labeling efficiency was 98 ± 2% as measured by TLC (85% methanol system) at time of preparation and 3 hr later.

Optimization in vitro. The optimum ratio of the individual components of the ^{99m}Tc-Sn·EHDP bone scanning agent was determined by sorption measurements of the Tc-Sn·EHDP radiotracer complex on synthetic hydroxyapatite (Molar Ca/P = 1.65, 3.2% H_2O: from Stauffer Chemical Co., New York). Hydroxyapatite (HA) was used as an in vitro skeletal model, and either EHDP or $SnCl_2$ were alternately varied while holding the other component constant.

To 50 ml of water, 100 mg of HA was added and continuously dispersed with a stirring bar holding pH constant without buffer at 7.4 using a Radiometer pH stat instrument (Copenhagen, Denmark). After 10 min, 1 ml of the Tc-Sn·EHDP radiotagged complex prepared as above was added to the HA-water slurry and allowed to equilibrate for a further 10 min. The slurry was then filtered through a 0.45-micron Millipore filter using an all-glass filtration system. A 1-ml aliquot of the filtrate was collected in a vial. The filter was dried with a heat lamp, the HA scraped off and dissolved in 6 *N* HCl and diluted to 1 ml in a similar vial. One milliliter of the initial Tc-Sn·EHDP radiotagged complex was used as a reference standard. The filtrate, HA, and standard were then radioassayed.

TABLE 1. PERCENT OF ^{99m}Tc-Sn·EHDP-1-^{14}C* SORBED ON HYDROXYAPATITE IN VITRO AS A FUNCTION OF EHDP CONCENTRATION

EHDP (mg/ml)	Percent of dose†	
	^{99m}Tc	EHDP-1-^{14}C
0.1	99	97
0.25	97	97
0.50	97	97
1.0	96	95
2.5	40	35

* 0.02 mg $SnCl_2$/ml.
† Average value of 3 experiments at each EHDP concentration.

TABLE 2. PERCENT OF ^{99m}Tc-^{113}Sn·EHDP* SORBED ON HYDROXYAPATITE IN VITRO AS A FUNCTION OF $^{113}SnCl_2$ CONCENTRATION

$^{113}SnCl_2$ (mg/ml)	Percent of dose	
	^{99m}Tc	^{113}Sn
0.01	91	81
0.02	95	93
0.05	91	90
0.1	84	88

* 1.0 mg EHDP/ml.

Dual experiments were conducted using ^{99m}Tc-^{113}Sn·EHDP and ^{99m}Tc-Sn·EHDP-1-^{14}C to permit the assay of the individual components of the ^{99m}Tc-^{113}Sn·EHDP-1-^{14}C. The gamma-emitting radionuclides were analyzed with a Ge(Li) gamma spectrometer system by integrating the area under the 140-keV photopeak of ^{99m}Tc and the 255-keV photopeak of ^{113}Sn. The high-resolution (1.94-keV FWHM for 1.33 keV) Ge(Li) detector easily resolved the 255-keV photopeak of ^{113}Sn and minimized the Compton effect from the ^{113m}In daughter. To assay the labeled EHDP, the ^{99m}Tc was counted and allowed to decay before complete combustion of the samples and analysis with the beta spectrometer (high temperature oxygen combustion train with trapping of $^{14}CO_2$ in a 1:7 ethanolamine:methyl cellosolve mixture).

Distribution in vivo. The tissue distribution of the radiotagged components of the bone scanning agent was evaluated in Sprague-Dawley strain female rats (200–250 gm). After an overnight fast, the rats were placed in Plexiglas chambers and anesthetized with Metofane (Pitman-Moore). The underside of the anesthetized rat's neck was shaved and an incision 1 cm long was made at the junction of the scapula and the rib cage. The jugular vein was exposed by parting the tissues with a hemostat, and a 0.5-ml injection of Tc-Sn·EHDP radiotagged complex was made directly into the vein. The incision was closed with a small wound clip, and the rat was allowed to recover from the anesthesia. Water was offered ad libitum, and the rats were sacrificed by decapitation at 3 and 24 hr after injection. Whole organs (bladder, kidneys, liver, spleen, lungs, brain, gonads), bones (femur, tibia, jaw, skull), femur bone marrow, muscle (back, femur, jaw), and carcass were removed, weighed, and placed in scintillation vials for radioassay of ^{99m}Tc. Urine and feces were collected over the entire experimental period. All the samples were initially scanned for ^{99m}Tc. Samples with high level of radioactivity, greater than 10% instrumental deadtime, were allowed to decay before counting to eliminate spectral shifting of the photopeaks. The ^{113}Sn and ^{14}C were assayed after the decay of the short-lived ^{99m}Tc. As in the in vitro studies, ^{113}Sn counts were determined with the gamma spectrometer and thereafter the samples were converted to $^{14}CO_2$ and analyzed on the beta spectrometer. The percent of dose per tissue or percent dose per gram of sample was determined by standards prepared from the administered ^{99m}Tc-Sn·EHDP-1-^{14}C or ^{99m}Tc-^{113}Sn·EHDP solutions.

RESULTS

Studies in vitro. The optimal concentration of EHDP for 0.02 mg $SnCl_2$, as measured from the sorption of ^{99m}Tc-Sn·EHDP-1-^{14}C on HA, was found to be between 0.1 mg and 1.0 mg EHDP/ml. These studies are summarized in Table 1. The 0.02 $SnCl_2$/ml used in the EHDP optimization was determined from concentration studies (0.01–0.1 mg as $^{113}SnCl_2$) with ^{99m}Tc-^{113}Sn·EHDP at 1 mg EHDP/ml and are shown in Table 2. The formulations chosen for the in vivo studies were the 1 mg EHDP + 0.02 mg $SnCl_2$ per mil (50:1) and 0.25 mg EHDP + 0.02 mg $SnCl_2$ per ml (12:1).

Studies in vivo. The results of the distribution studies in normal rats at 3 and 24 hr after administration of the bone scanning agent are summarized in Table 3 for ^{99m}Tc-Sn·EHDP-1-^{14}C at the 50:1

TABLE 3. ORGAN DISTRIBUTION OF ^{99m}Tc-Sn·EHDP-1-^{14}C FOR 50:1 AND ^{99m}Tc-^{113}Sn·EHDP-1-^{14}C FOR 12:1 WEIGHT RATIOS (AT 3 AND 24 HR, 0.02 mg $SnCl_2$/ml)

	Percent dose at 50:1 (EHDP:$SnCl_2$)				Percent dose at 12:1 (EHDP:$SnCl_2$)					
	3 hr		24 hr		3 hr			24 hr		
Organ	^{99m}Tc	EHDP-^{14}C	^{99m}Tc	EHDP-^{14}C	^{99m}Tc	^{113}Sn	EHDP-^{14}C	^{99m}Tc	^{113}Sn	EHDP-^{14}C
Bladder	0.10	0.03	<0.01	0.00	0.10	0.03	0.25	<0.01	0.00	0.01
Kidneys	0.56	0.31	0.64	0.25	0.72	0.41	0.42	0.81	0.45	0.30
Liver	0.22	0.72	0.14	0.14	0.20	0.40	0.20	0.76	0.31	1.90
Spleen	0.04	0.49	0.01	0.02	0.03	0.04	0.02	0.02	0.02	0.03
Heart	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0.01	0.02
Lungs	0.04	0.02	0.01	0.01	0.06	0.05	0.05	0.09	0.03	0.05
Brain	0.01	0.01	<0.01	<0.01	0.01	0.02	0.01	0.01	0.01	0.01
Gonads	0.02	0.03	0.02	0.02	0.07	0.02	0.07	0.02	0.01	<0.00
Femur (one)	1.72	2.15	1.50	1.98	1.76	2.12	2.12	1.30	2.08	1.79
Tibia (one)	0.95	1.15	1.28	1.53	1.56	1.78	1.82	1.06	1.72	1.30
Jaw bone	0.81	0.95	0.75	0.91	1.09	0.63	—	0.82	0.71	0.99
Skull bone	0.28	0.37	0.33	0.39	0.42	0.36	0.56	0.31	0.32	0.38
Urine	48.0	38.0	51.0	42.1	58.2	—	48.0	61.0	42.6	52.0
Marrow	0.02	0.01	<0.01	<0.01	0.01	<0.01	0.03	<0.01	<0.01	<0.01
Carcass	38.0	35.0	31.2	38.3	40.0	32.7	56.0	31.9	31.5	41.0
Feces	0.72	0.48	0.28	1.79	1.34	3.3	—	1.43	0.17	0.52
	Percent of dose per gram									
Bone marrow	0.02	0.01	0.01	0.01	0.01	<0.01	0.03	<0.01	<0.01	<0.01
Back muscle	<0.01	—	<0.01	—	—	—	—	—	—	—
Femur muscle	<0.01	0.01	0.02	0.05	<0.01	0.03	<0.01	0.03	0.04	0.06
Jaw muscle	<0.01	<0.01	<0.01	<0.01	0.01	0.07	0.02	<0.01	0.02	<0.01
Blood	<0.01	<0.01	<0.01	<0.01	<0.01	0.02	<0.01	<0.01	<0.01	<0.01

Mean value ±20% of three Sprague-Dawley rats for the kidneys, liver, skeleton, and urine. Where values were 0.1% of dose or less, larger deviations were obtained.

ratio, and ^{99m}Tc-^{113}Sn·EHDP-1-^{14}C (^{99m}Tc-^{113}Sn·EHDP and ^{99m}Tc-Sn·EHDP-^{14}C) at the 12:1 ratio.

Using muscle tissue from the femur region, back, and jaw as representative of soft-tissue uptake, the percent of ^{99m}Tc dose per gram retained by these tissues was determined. The 3- and 24-hr values for these soft tissues were all 0.03% of dose per gram or lower for ^{99m}Tc at both 12:1 and 50:1 (EHDP: $SnCl_2$) weight ratio. Bone marrow obtained from femurs at both 3 and 24 hr had 0.02% dose/gm or lower of the administered ^{99m}Tc. The distribution (retention) in total soft tissue and organs accounted for less than 2% of the dose at 3 hr postinjection. The skeletal uptake at 3 hr as measured from the femur, tibia, jaw, skull, and the carcass, which is essentially all skeleton after the removal of the organs, accounted for approximately 42–45% of the total ^{99m}Tc dose. The urine accounted for the remainder of the administered dose. Feces were collected for 24 hr for both ratios, and 0.2–3.3% was detected. The high urine excretion value leads us to suspect that the feces values are probably high as a result of urine contamination.

A composite camera picture of a rat made with the pinhole collimator 3 hr after intravenous injection at the 50:1 ratio is shown in Fig. 1. Little soft-tissue retention is evident in the composite, and the uptake is clearly limited to the skeleton.

The total blood retention at 3 hr of both the ^{14}C-EHDP (at the 12:1 and 50:1 weight ratio EHDP: $SnCl_2$) and ^{113}Sn (at the 12:1 ratio) was less than 2% of the administered dose (greater than 98% cleared from the blood). The ^{99m}Tc value for both

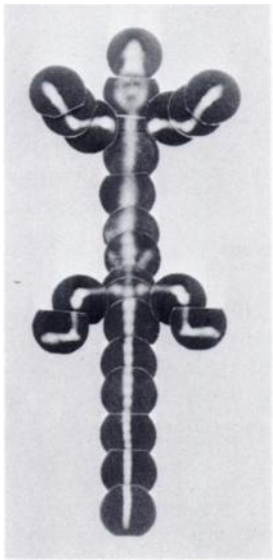


FIG. 1. Composite ^{99m}Tc gamma camera picture of skeleton of normal growing Sprague-Dawley rat. Pictures were taken approximately 3 hr after administration of ^{99m}Tc-Sn·EHDP complex using ⅛-in. pinhole collimator.

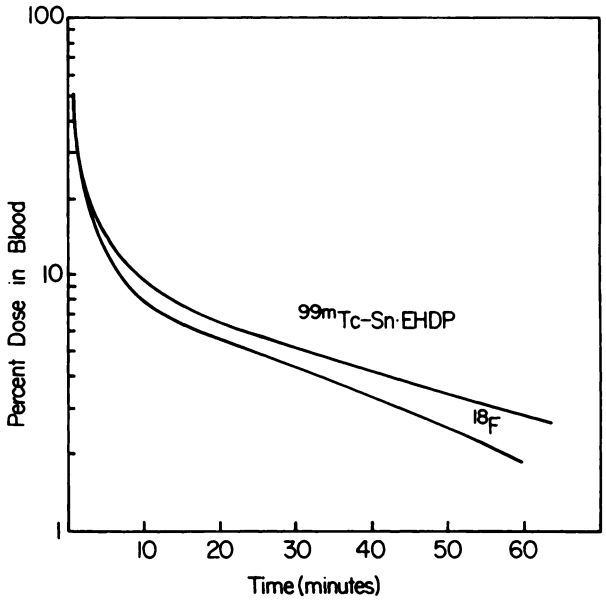


FIG. 2. Average blood clearance of ^{99m}Tc and ^{18}F from three Sprague-Dawley rats. Technetium-99m-Sn·EHDP complex or ^{18}F ion were given intravenously as bolus injection into jugular vein of normal rat. Blood was serially sampled, counted directly and corrected for decay, and plotted as percent of dose in total blood volume of rats. Standard deviation is 2–5% for 0–5 min clearance and less than 0.5% at 5–60 min.

ratios was approximately 1% at 3 hr and decreased to less than 0.1% at 24 hr after injection. The total blood retention in rats from 0 to 60 min, as percent of ^{99m}Tc dose in whole blood, after intravenous administration of the ^{99m}Tc-Sn·EHDP complex is illustrated in Fig. 2. It is evident that the agent is rapidly cleared from the blood. For comparative purposes, the ^{18}F-fluoride (Medi+Physics) rate of clearance was also measured in Sprague-Dawley rats of similar age, sex, and weight. Spectral stripping of the blood curves for ^{99m}Tc-Sn·EHDP and ^{18}F in the rat indicate a curve composed of at least three exponential components: a very short component, a measurable component (6–8 min), and a longer component of approximately 35 min. This rapid blood clearance permits excellent skeletal imaging at 3 hr after administration of the ^{99m}Tc-Sn·EHDP agent.

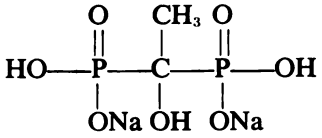
DISCUSSION

The bone scanning agent ^{18}F-fluoride has been shown to be important in the initial evaluation of patients with malignant neoplasm to determine whether curative or palliative therapy is the management of choice. Although ^{18}F-fluoride produces high-quality scintigraphs of osseous disorders, the principle limitations are its availability, restricted by its short half-life, cost, and high-energy gamma rays (510 keV), which are difficult to collimate and detect efficiently with the Anger camera.

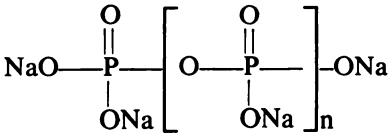
The phosphonate, EHDP, and the polyphosphates

use a more ideal isotope, ^{99m}Tc, and consequently hold promise as effective scanning agents. Structurally the compounds can be shown as follows:

(I) Diphosphonate (Na_2EHDP)



(II) Polyphosphate



(n = number of phosphate groups)

If n = 1 in II above, then we have pyrophosphate ($Na_4P_2O_7$); if n = 2, the well-known tripolyphosphate ($Na_5P_3O_{10}$), if n > 2, condensed phosphates. The most significant difference between these two types of compounds (I and II) is that II is readily chemically hydrolyzable and is also hydrolyzed in vivo, presumably by the action of pyrophosphatase enzyme (alkaline phosphatase) (*14*). In the case of the phosphonate, disodium ethane-1-hydroxy-1, 1-diphosphonate, however, the P-C-P bonds are very stable, both chemically (*4*) and to the action of pyrophosphatase enzyme (*14*). Another difference between the condensed phosphates and phosphonates is in the synthesis. The "poly"-compounds form a range of molecular weights, and reproducible synthesis of a narrow range of molecular weights or a unique molecular size is difficult. In the case of the phosphonates, however, a single, highly purified compound, such as EHDP, can be obtained which is stable both chemically (in vitro) and enzymatically (in vivo).

The data from Table 3 indicate that the Tc, Sn, and EHDP appear to be deposited on bone in roughly equal percentages of dose. A consistent ratio of 1.2 to 1.3 for EHDP-1-^{14}C/^{99m}Tc (Table 4) was found for the skeletal samples at 3 hr and remained nearly the same at 24 hr after administration, which suggests that the agent is delivered to the skeleton and remains there as a unit. It is the in vivo stability that enables the ^{99m}Tc-Sn·EHDP bone scanning agent to travel in the blood as a unit until either sorbed on bone or excreted in the urine. Polyphosphates, on the contrary, would be subject to enzymatic hydrolysis in the blood and particularly at the site of bone pathology where alkaline phosphatase (pyrophosphatase) activity would be expected to be excessively high. The slightly greater than one ratio may arise from a difference in sorption between the Sn·EHDP complex and the free EHDP assuming all the reduced ^{99m}Tc is complexed to the "carrier" Sn·EHDP. A slight hindrance of sorption of the Sn·EHDP complex is possibly a result of a difference in its passive diffusion to the bone because of the size of the molecular complex or to charge differences on the diffusing species.

TABLE 4. SKELETAL ^{14}C/^{99m}Tc* FOR 12:1 AND 50:1 WEIGHT RATIOS (EHDP:$SnCl_2$) AT 3 AND 24 HR

	3 hr		24 hr	
Skeletal sample	12:1	50:1	12:1	50:1
Femur	1.2	1.2	1.4	1.3
Tibia	1.2	1.2	1.2	1.2
Jaw bone	—	1.2	1.2	1.2
Skull bone	1.3	1.3	1.2	1.2

* Ratio of % of ^{14}C dose to % of ^{99m}Tc dose on the skeleton.

The amount of ^{99m}Tc-Sn·EHDP administered to the animals and the appropriate amount for man are very low. The total dose for EHDP is in the range of 0.5–1 mg for a child and 1–2 mg for an adult. The material, EHDP, has been used in a large number of patients who have various bone diseases and calcific disorders. Patients with myositis ossificans progressiva given 10–20 mg EHDP/kg/day oral dose have shown no adverse effects (*15*). The amount of tin deposited on the human skeleton would be half the administered dose, approximately 10 μg. Since tin is already present at relatively high concentrations in bone (0.5 ppm Sn) (*16*), this small addition (0.0014 ppm for a 70-kg man) would not be expected to present any toxicological problem.

Since the introduction of EHDP for bone scanning (*5,6*), the clinical studies (*10–12*) indicate that the diphosphonate complex, Sn·EHDP, appears to be a safe, consistent, and stable bone scanning agent when combined with ^{99m}Tc and could become a routine part of diagnostic nuclear medicine in both large and small institutions, independent of geographic location or special instrumentation.

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REFERENCES

1. TREADWELL A DEG, LOW-BEER BUA, FRIEDELL HL, et al: Metabolic studies on neoplasm of bone with the aid of radioactive strontium. *Am J Med Sci* 204: 521–530, 1942

2. SUBRAMANIAN G, MCAFEE JG: A new complex of ^{99m}Tc for skeletal imaging. *Radiology* 99: 192–196, 1971

3. SUBRAMANIAN G, MCAFEE JG, BELL EG, et al: ^{99m}Tc-labeled polyphosphate as a skeletal imaging agent. *Radiology* 102: 701–704, 1972

4. FRANCIS MD: The inhibition of calcium hydroxyapatite crystal growth by polyphosphonates and polyphosphates. *Calcif Tissue Res* 3: 151–162, 1969

5. TOFE, AJ, FRANCIS MD: In vitro optimization and organ distribution studies in animals with the bone scanning agent ^{99m}Tc-Sn·EHDP. *J Nucl Med* 13: 472, 1972

6. YANO Y, MCRAE J, VAN DYKE DC, et al: ^{99m}Tc-labeled Sn(II)-diphosphonates. A new bone scanning agent. *J Nucl Med* 13: 480, 1972

7. CASTRONOVO FP, CALLAHAN RJ: New bone scanning agent: ^{99m}Tc-labeled 1-hydroxy-ethylidene-1, 1-disodium phosphonate. *J Nucl Med* 13: 823–827, 1972

8. SUBRAMANIAN G, MCAFEE JG, BLAIR RJ, et al: ^{99m}Tc-EHDP: A potential radiopharmaceutical for skeletal imaging. *J Nucl Med* 13: 947–950, 1972

9. YANO Y, MCRAE J, VAN DYKE DC, et al: ^{99m}Tc-labeled stannous ethane-1-hydroxy-1, 1-diphosphonate: A new bone scanning agent. *J Nucl Med* 14: 73–78, 1973

10. WELLMAN NH, TOFE AJ, BROWNE A, et al: Optimizing of a new kit—prepared skeletal imaging agent, ^{99m}Tc-Sn·EHDP, as compared to ^{18}F. In *New Developments in Radiopharmaceuticals and Labeled Compounds.* Vienna, IAEA, 1973

11. SILBERSTEIN EB, SAENGER EL, TOFE AJ, et al: Imaging of bone metastases with ^{99m}Tc-Sn·EHDP (diphosphonate), ^{18}F, and skeletal radiography. *Radiology* 107: 551–555, 1973

12. PENDERGRASS HP, POTSAID MS, CASTRONOVO FP: The clinical use of ^{99m}Tc-diphosphonate (HEDSPA). *Radiology* 107: 557–562, 1973

13. QUIMBY OT, PRINTICE JB: Procter & Gamble Co, U.S. Patent 3400149, 1968

14. RUSSELL RGG, MÜHLBAUER RC, BISAZ S, et al: The influence of pyrophosphate, condensed phosphates, phosphonates and other phosphate compounds on the dissolution of hydroxyapatite in vitro and on bone resorption induced by parathyroid hormone in tissue culture and in thyroparathyroidectomized rats. *Calcif Tissue Res* 6: 183–196, 1970

15. GEHO WB, WHITESIDE JA: Experience with disodium etidronate on diseases of ectopic calcification. Proc. Internatl. Symposium on Metab Bone Diseases, Detroit, Michigan (In press)

16. KEHOE RA, CHOLAK J, STORY RV: A spectrochemical study of the normal ranges of concentration of certain trace metal in biological materials. *J Nutr* 19: 579–592, 1940

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The Scientific Program Committee welcomes the submission of abstracts for 12-minute papers from technologists for the meeting. Abstracts must be submitted on an abstract form similar to the form for general scientific papers. The length must not exceed 400 words and the format of the abstracts must follow the requirements set down for all abstracts for the scientific program. This year's form will be available from the Technologist Section, Society of Nuclear Medicine, 305 East 45th Street, New York, N.Y. 10017.

In addition, the Program Committee invites abstracts for papers from students presently enrolled in schools of nuclear medicine technology. Special time will be set aside for a student session.

Send abstract form to: Richard S. Pollack, M.S., Nuclear Medicine Department, John F. Kennedy Community Hospital, James Street, Edison, New Jersey 08817.