CYCLOTRON-PRODUCED ^{157}Dy COMPARED WITH ^{18}F FOR BONE SCANNING USING THE WHOLE-BODY SCANNER AND SCINTILLATION CAMERA

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Scanning with bone-seeking radiopharmaceuticals has been shown to be a useful procedure in the early detection of metastic bone lesions. Greenberg, who scanned with ^{47}Ca and ^{85}Sr, states that the time between abnormal scan findings and radiographic or histological confirmation varies from 34 to 164 days (*1*). The principal bone-seeking agents are ^{47}Ca, ^{85}Sr, ^{87m}Sr, and ^{18}F. The long half-life of ^{85}Sr (65 days) and the high gamma-ray energy of ^{47}Ca (1.31 MeV) make these radionuclides less satisfactory than ^{18}F (*2,3*) and ^{87m}Sr (*4,5*). These short-lived radionuclides permit larger injected doses with higher counting rates and decreased radiation dose.

Evaluations of ^{18}F, ^{87m}Sr, and ^{85}Sr for bone scanning have been made by Ronai (*6*), French (*7*), and Spencer (*8*). These studies generally agree with Weber's findings that ^{18}F is the isotope of choice for bone scanning because of reduced radiation dose, increased counting rate, rapid clearance from plasma and soft tissue (4–5 times as fast as other bone-seeking radionuclides), and a high ratio of uptake by lesion to uptake by normal bone (*9*). Strontium-87m appears to be nearly as good as ^{18}F except for a slower clearance from the plasma. The availability of ^{18}F is limited to areas near a cyclotron or nuclear reactor, whereas ^{87m}Sr is obtained from its 3.3-day parent ^{87}Y in a generator.

We have used both reactor- and cyclotron-produced ^{18}F for bone scanning with the Anger Mark II Whole-Body Scanner described previously (*10*) and the positron scintillation camera (*11*). Over a period of 7 years we have studied 270 patients. Although ^{18}F is useful for obtaining scans showing bone tumors, it is less than an ideal nuclide because the 110-min half-life restricts availability and the 511-keV gamma-ray emissions are difficult to collimate and detect efficiently with conventional gamma-ray cameras and scanners.

In the search for a bone-scanning radionuclide with a more convenient half-life and a more useful gamma-ray emission, we have investigated ^{157}Dy, a heavy lanthanon of the rare earth group of elements. Durbin reported that the heavier lanthanons (Tb, Dy, and Lu) are taken up 50–60% in bone when injected intramuscularly as a citrate complex (*12*). O'Mara has investigated the distribution of a number of rare earth radionuclides (^{153}Sm, ^{171}Er, and ^{177}Lu) as HEDTA chelates and found about 50% of the injected dose taken up in the bone of rabbits (*13*).

Preliminary studies in animal and human subjects indicate that when ^{157}Dy is administered as an HEDTA (N-hydroxy-ethylenediaminetriacetic acid) chelate, it localizes primarily in the bone (about 50% of the injected dose) and the remainder is excreted by the kidneys in much the same manner as ^{18}F.

MATERIALS AND METHODS

Radionuclides. Dysprosium-157 ($T_{1/2}$ 8.1 hr) decays 100% by electron capture to ^{157}Tb ($T_{1/2}$, 150 years) which then decays 100% by electron capture to stable ^{157}Gd. The gamma emission of ^{157}Dy is essentially monoenergetic 326 keV (91% abundant). Because of the great difference in half-life between ^{157}Dy and the daughter ^{157}Tb, the amount of ^{157}Tb produced by decay of ^{157}Dy is negligible (about 10^{-3} μCi ^{157}Tb from 1 mCi ^{157}Dy) in calculating the radiation dose from ^{157}Dy. Figure 1 shows the decay scheme and the gamma spectrum of ^{157}Dy.

Dysprosium-157 is produced by irradiating 300 mg of ^{159}Tb (100% abundant) as $TbCl_3 \cdot 6H_2O$ with 30-MeV protons, $^{159}_{65}$Tb(p,3n)$^{157}_{66}$Dy. The alternative nuclear reactions of (p,2n) and (p,4n) produce the stable isotopes of ^{158}Dy and ^{156}Dy, respectively.

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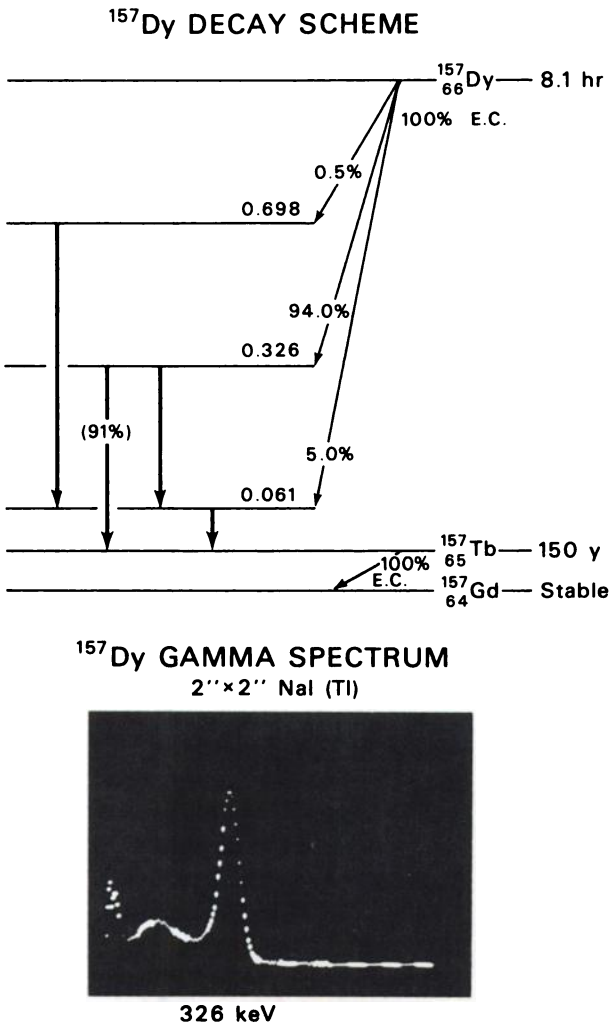

FIG. 1. Decay scheme and gamma spectrum of ^{157}Dy.

Contaminating radionuclides produced by the irradiation were identified by gamma-spectrum analysis using a 400-channel analyzer and a 2 × 2-in. NaI(Tl) crystal. Decay curves of the contaminating radionuclides were obtained over a period of 8 months to determine the half-life of radionuclides produced from the proton irradiation of ^{159}Tb (99.9% pure).

The production yield of ^{157}Dy from an irradiation with 30-MeV protons and 16 μA of beam current is 2.48 mCi/μA-hr or 39.6 mCi/hr (mean values from 11 production runs). Relative concentrations of nuclides that contaminate ^{157}Dy are $< 10^{-4}$ parts of ^{156}Tb ($T_{1/2}$, 5.1 days decaying 99% by electron capture to stable ^{156}Gd) and $< 10^{-5}$ parts of ^{160}Tb ($T_{1/2}$, 72.1 days decaying 100% by β^- emission to stable ^{160}Dy).

Fluorine-18 ($T_{1/2}$, 110 min) decays 3% by electron capture and 97% by positron emission with accompanying 511-keV annihilation gamma rays. Fluorine-18 is produced by cyclotron irradiation of 50 ml of pure H_2O in a quartz glass target vessel with 65-MeV alpha particles by the $^{16}O(\alpha,pn)^{18}F$ and $^{16}O(\alpha,2n)^{18}Ne \xrightarrow{\beta+} {}^{18}F$ reactions. The production yield of ^{18}F from an irradiation with 65-MeV alpha particles is 19 mCi/μA-hr or 116 mCi/hr (*14*).

The relative cyclotron production cost is about the same for either ^{18}F or ^{157}Dy when allowance is made for ten times greater decay loss for ^{18}F compared with ^{157}Dy 8 hr after the end of irradiation.

Chemistry. The $TbCl_3 \cdot 6H_2O$ target material is washed from the aluminum target plate with 10 ml of H_2O and diluted to 20 ml with 1.0 *N* HCl acid. This solution of ^{157}Dy-$TbCl_3 \cdot H_2O$, containing about 2.3 mCi ^{157}Dy/ml and 4.02×10^{-2} m*M* Tb/ml (6.4 mg Tb/ml), is filtered through 0.22-micron Millipore filter. An aliquot of the target solution is taken to give the desired activity, and HEDTA is added to give a desired molar ratio to terbium. Sodium hydroxide is added dropwise to pH 6–7 and calcium gluconate-heptonate (Abbott, sterile solution 20% w/v) is added to give a desired molar ratio of calcium to HEDTA. A typical preparation of 20:1 HEDTA to terbium and 2:1 calcium to HEDTA contains 475 μCi ^{157}Dy, 1.15 mg terbium, 40 mg HEDTA, and 11.5 mg calcium per ml.

Dysprosium-157-HEDTA was prepared in different molar ratios of HEDTA to terbium (which acts as a dysprosium "carrier ion") and different molar ratios of calcium to HEDTA to determine the effects of the concentrations of terbium, HEDTA, and calcium on the ratio of ^{157}Dy uptake in bone to blood and soft tissue.

The reagent solutions and glassware used for the preparation of ^{157}Dy-HEDTA are sterilized either by Millipore filtration or by autoclaving. In some preparations chemical separation of ^{157}Dy from the terbium target material was done by using cation exchange resin AG 50 × 4 (Bio-Rad) 100–200 mesh, NH_4^+ form, and packed in a glass column 1.6 cm × 18.4 cm. The eluant solution is α-hydroxyisobutyric acid; 0.4 *M*, pH 3.4 (*15*).

Terbium-160 is used as the tracer for terbium elution. The ion exchange column and eluant solution are maintained at 70°C during the elution at a flow rate of 1 ml/min. A series of 5-ml fractions are collected with an automatic fraction collector. Two detector probes are used; one to monitor the ^{157}Dy and the other to monitor the ^{160}Tb activity as it drops from the tip of the elution column. A chart recorder is used to trace the activity of ^{157}Dy and ^{160}Tb collected in each fraction. Dysprosium-157 comes off first in about 40–50 ml of elution volume. Terbium-160 begins to come off near the end of the ^{157}Dy

elution. Some ^{157}Dy is lost in discarding the overlapping ^{160}Tb elution volume. The separation procedure requires 4–6 hr.

RESULTS AND DISCUSSION

Animal studies. Dysprosium-157-HEDTA uptake in rat tissue was determined in 200-gm Sprague-Dawley rats. Figure 2 shows the distribution of ^{157}Dy-HEDTA in rat tissue [blood, lungs, liver, kidneys, spleen, muscle over sternum, muscle over femur, and bone (femur)]. The results are expressed as percent per gram of tissue 2 hr after intravenous administration of various molar ratios of HEDTA to terbium. The preparations were injected at pH 6–7 with an excess of calcium to HEDTA. In rats the higher molar ratio of HEDTA to terbium enhances clearance from the blood and uptake in bone while minimizing the uptake in liver. A molar ratio of 20:1 HEDTA to ^{157}Dy-Tb enhances bone uptake and reduces the level of blood activity.

Preparations of ^{157}Dy-HEDTA were also studied in seven beagle dogs and five rhesus monkeys. Blood disappearance half-times were determined and compared with half-times for ^{157}Dy-HEDTA both with and without terbium "carrier" as well as for various amounts of HEDTA and calcium. The clearance of ^{157}Dy from the blood was determined by taking 1-ml blood samples periodically after administration of the radionuclide and counting in a deep well counter with a NaI(Tl) crystal and multichannel analyzer. Blood disappearance half-times were obtained from a semilogarithmic plot of the data. Table 1 gives a summary of the blood-disappearance half-times for ^{157}Dy-REDTA in beagle dogs and rhesus monkeys.

These results in dogs indicate that a molar ratio of 20:1 HEDTA to Tb-^{157}Dy is sufficient excess to bind the ^{157}Dy to HEDTA in preference to binding to the blood plasma proteins. In contrast the results with monkeys at 10:1 molar ratios of HEDTA:Tb indicate the binding of ^{157}Dy to plasma proteins.

TABLE 1. ^{157}Dy-HEDTA ($T_{1/2}$ BLOOD DISAPPEARANCE) FOR VARIOUS CONCENTRATIONS OF HEDTA AND Ca IN DOGS AND MONKEYS

Ratio HEDTA:Tb	Ratio Ca:HEDTA	Blood $T_{1/2}$ (min) (fast)	Blood $T_{1/2}$ (min) (slow)
Beagle dogs			
20:1	1:1	8.5	50
20:1	2:1	13	77
20:1	3:1	11.5	96
Tb "free"		10	79
Rhesus monkeys			
10:1	1:1	15	265
10:1	2:1	blood activity constant	
20:1	2:1	7	26

The calcium-to-HEDTA ratio, on the other hand, appears to influence the extraction of ^{157}Dy from the HEDTA binding sites into bone-binding sites, as shown by the increasing blood disappearance half-times with increasing calcium-to-HEDTA ratios in dogs. This effect can also be seen in the monkeys: an increase in calcium-to-HEDTA ratio prevents the ^{157}Dy from being extracted as efficiently by bone, and at the 10:1 HEDTA and 2:1 calcium ratios the ^{157}Dy appears to be bound to proteins in the blood plasma and remains in the blood pool, whereas the 1:1 calcium-to-HEDTA ratio exhibits a 265-min $T_{1/2}$ for disappearance from the blood.

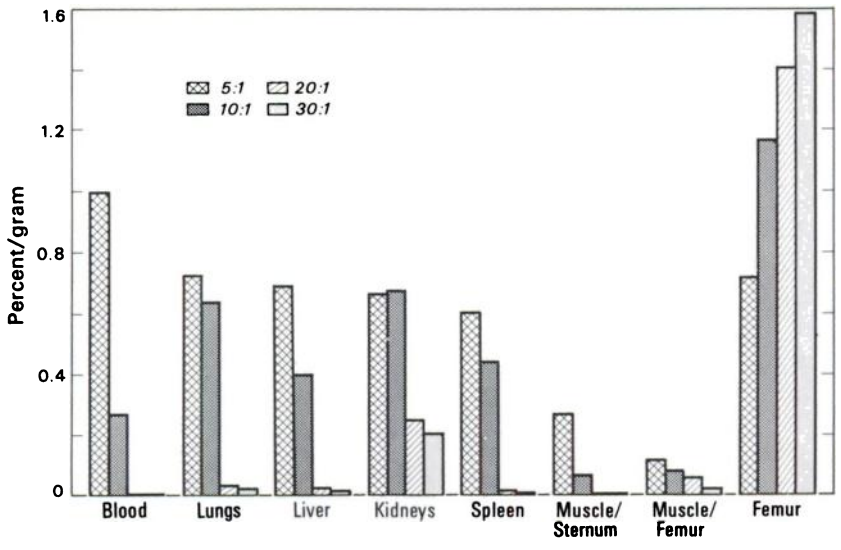

FIG. 2. Distribution of ^{157}Dy-HEDTA in rat tissue 2 hr after intravenous administration of 5:1, 10:1, 20:1, and 30:1 molar ratios of HEDTA to terbium.

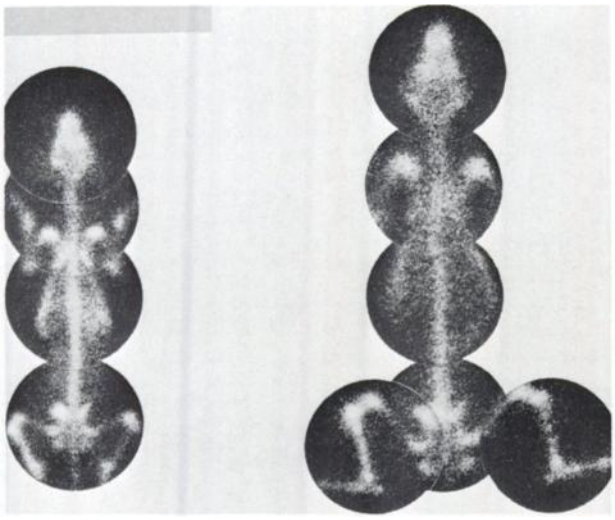

FIG. 3. Posterior views of dog with lesion in left tibia; ^{157}Dy-HEDTA scintillation-camera pictures (left) and ^{18}F positron-camera pictures (right). Note enlargement of ^{18}F positron camera image on right compared with ^{157}Dy scintillation camera picture on left.

The removal of "carrier" terbium did not enhance the disappearance half-time of ^{157}Dy from the blood. This result is contrary to what would be expected from Tb-free ^{157}Dy because terbium and calcium are very likely to be in competition with ^{157}Dy for the bone binding sites. However, the competition of terbium, calcium, and ^{157}Dy for binding sites on the blood plasma proteins would explain the unexpected enhancement of ^{157}Dy clearance from the blood when terbium "carrier" is present.

Toxicity studies were done by administering 100 times the proposed human dose of terbium, HEDTA, and calcium gluconate in two rats, one dog, and one monkey. There were no visible adverse reactions.

Scintillation-camera pictures and whole-body scans were taken 2–3 hr after intravenous administration to determine the distribution of ^{157}Dy-HEDTA and Na^{18}F.

Figure 3 shows the distribution of 1 mCi ^{157}Dy-HEDTA (20:1) and 150 μCi ^{18}F in a dog with a lesion in the left tibia produced by curetting the inside of the bone. Increased uptake at the lesion site is demonstrated with both radionuclides.

Patient studies. Twenty-two patients were studied at Donner Laboratory from June 6, 1970, to December 21, 1970. Further studies of patients were also done with the cooperation of Weber at Kaiser Hospital, Oakland, California, and Kriss, Stanford University Medical Center, Stanford, California.

A typical administered dose to humans of 1.0 mCi of ^{157}Dy-HEDTA in a volume of 2.1 ml contained 2.4 mg terbium, 84.5 mg HEDTA, and 24.2 mg calcium.

Comparisons were made of ^{157}Dy-HEDTA and ^{18}F distribution in 9 of 22 patients with established malignancy. They were given 500–600 μCi of ^{18}F, and 3 hr later 22-min whole-body scans were obtained from the posterior view. In some patients positron scintillation-camera pictures were also obtained. One week later the patients returned to receive 1.0 mCi ^{157}Dy-HEDTA and were scanned under the same conditions as with ^{18}F. In some cases scintillation-camera pictures were taken using the ^{131}I (2.2-in.-thick) lead collimator. Each field of view was exposed for 5 min.

Table 2 summarizes the results for patients studied with ^{18}F and ^{157}Dy.

A 43-year-old female patient with cancer of the breast and metastases to the liver is shown in Fig. 4, which is a composite of scintillation-camera pictures. There is increased uptake of ^{157}Dy-HEDTA in the spine and pelvis. There is also some uptake in the right chest area and increased uptake in the distal end of the left femur.

Figure 5 shows the whole-body scan distribution of ^{18}F, ^{157}Dy, and ^{85}Sr in a 55-year-old male pa-

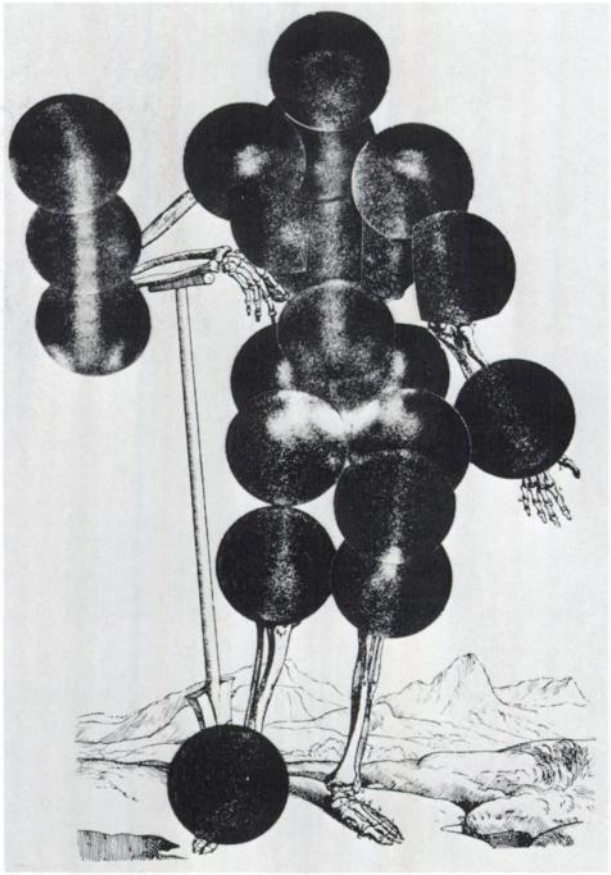

FIG. 4. ^{157}Dy-HEDTA scintillation camera picture of female patient with cancer of breast and metastases to liver. Anterior view (right) and posterior view of thoracic spine (left) note improved resolution of spine from posterior aspect.

tient with cancer of the lungs. All three radioisotopes show increased uptake in the right shoulder and right lateral rib cage, which corresponds to a fracture site. Increased uptake is also seen in the upper thoracic area near the spine and near the left rib cage. The increased uptake in the right lateral thoracic area corresponds to an incision site for thoracotomy.

The kinetics of ^{157}Dy-HEDTA was determined in three patients, two with normal and one with abnormal extraction of ^{157}Dy-HEDTA by the bone. The results are shown in Table 3. The mean normal excretion value of 44.5% of the injected dose compares with 22.5% excreted in urine at 3 hr for ^{18}F (*17*).

These limited data of the kinetics of ^{157}Dy-HEDTA in humans seem to indicate that relatively high blood levels and high excretion rates are associated with normal bone uptake, whereas abnormal or high bone uptake is reflected by low blood levels and reduced excretion of ^{157}Dy.

The radiation dose to a 70-kg human subject from 1.0 mCi of ^{157}Dy-HEDTA, assuming 50% uptake in bone, 50% excretion by the kidneys, and an effective half-life equal to the physical half-life in bone and 1 hr in the bladder and kidneys, is 0.158 rad to kidneys, 0.316 rad to bladder, and 0.144 rad to bone.

Information regarding the toxicity of terbium is rather limited. However, information regarding the lanthanide series of rare earth elements can be used for relative comparison. Mogilevskaya and Raikhlin (*16*) state that on intravenous administration of the chlorides of praseodymium, lanthanum, cerium, and neodymium the LD_{50} is 200–250 mg/kg in rabbits.

TABLE 2. RESULTS FROM SCANNING 22 PATIENTS AT DONNER LABORATORY WITH ^{157}Dy-HEDTA AND ^{18}F*

Patient/sex	Condition	^{157}Dy	^{18}F	^{85}Sr	Remarks
RB/M	Hepatoma? metastases	—	—		
VM/F	Postoperative CA of breast	—			
NJ/M	Multiple myeloma, osteoporotic disease		—		
LW/F	Bone tumor	+			Increased uptake R anterior thoracic
LS/F	CA esophagus, back trauma fx L-4-pain pelvis and hip	+			Increased uptake in three areas
CD/F	Old CA lung	+	+		Increased uptake T9-10; also in wrist due to sprain; increased uptake in thoracic spine
JA/M	CA lung—alcoholic	+	+	+	Increased uptake in R shoulder, R lateral rib cage, hip and thoracic spine—^{157}Dy, ^{85}Sr, ^{18}F
SH/F	Hodgkin's	+			Heavy concentration in sacroiliac joints—more in R
MH/F	Paget's	+			Increased uptake in sacroiliac joints
JE/M	Voorhees's disease L upper arm	+	+		Increased uptake in old fractured R femur
EJ/F	L radical mastectomy—supraclavicular lymph nodes	—			
GZ/F	Skeletal metastases from CA breast	+			Good visualization of lesions (lumbar spine)
MH/F	'61 mastectomy & oophorectomy; '70 L-4 collapse	+	+		Increased uptake: L-4 R of midline
RT/F	Hodgkin's	+			Increased uptake L knee, uptake L temporal skull and L scapula
GP/M	Bone metastasis; CA of Rt. lung	—			
MC/F	Breast CA; liver metastasis	—	—		
HG/M	Lymphosarcoma, pain hips and lower spine	+	+		Increased lumbar spine (normal after radiation therapy)
SM/F	Osteoporosis old fx T-6	—	—		Decreased bone blood flow No abnormal regional uptake
MB/F	Early myeloma	—			
KC/M	Possible lesion T6-9	—			

* (+) indicates abnormal bone scan; (—) normal bone scan.

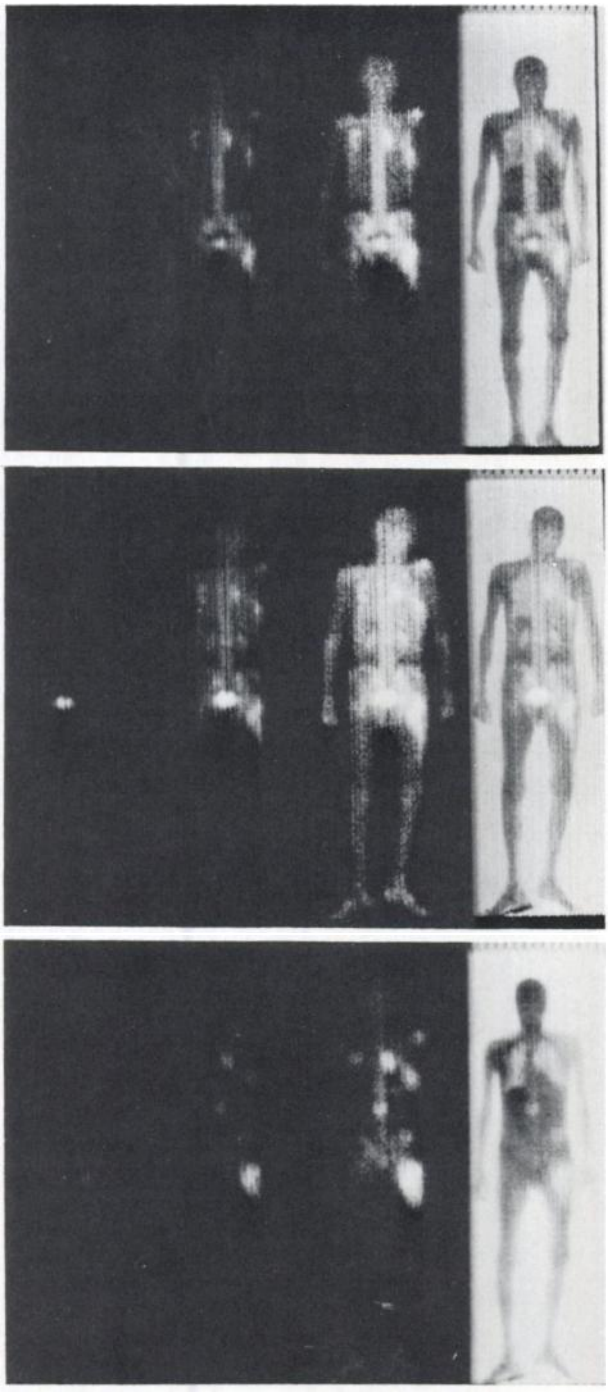

FIG. 5. Whole-body scan of male patient with cancer of lungs; ^{18}F scan (top), ^{157}Dy scan (middle), and ^{85}Sr scan (bottom). Note increased uptake in lumbar spine and at fracture site in right femur.

This is 7,000 times more than the human dose. Furthermore, when ^{157}Dy-Tb is administered as an HEDTA chelated compound, about 50% of the injected dose is rapidly excreted.

All initial studies were performed on patients with established malignancy.

For general clinical applications, ^{157}Dy should probably be separated from the terbium target material by the ion-exchange procedure described earlier. This will produce ^{157}Dy free of terbium and permit very low concentrations of HEDTA and calcium.

SUMMARY

Some of the advantages of ^{157}Dy for bone scanning are 8.1-hr half-life, high yield of 326-keV photons, and decay by electron capture. When ^{157}Dy is administered as an HEDTA chelate in a molar ratio of 20:1 of HEDTA to terbium, uptake of activity is primarily in the bone with increased uptake in bone lesions. With ^{157}Dy-HEDTA, clearance from blood and soft tissues occurred within 3–5 hr after intravenous administration compared with 2–3 hr with ^{18}F. The slower clearance of ^{157}Dy as well as a relatively lower extraction efficiency of bone make ^{157}Dy a somewhat poorer bone-scanning agent than ^{18}F.

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REFERENCES

1. GREENBERG EJ, WEBER DA, POCHACZEWSKY R, et al: Detection of neoplastic bone lesions by quantitative scanning and radiography. *J Nucl Med* 9: 613–620, 1968

2. BLAU M, NAGLER W, BENDER MW: Flourine-18. A new isotope for bone scanning. *J Nucl Med* 3: 332–334, 1962

3. VAN DYKE DC, ANGER HO, YANO Y, et al: Bone blood flow shown with ^{18}F and the positron camera. *Amer J Physiol* 209: 65–70, 1965

4. MYERS WG: Radiostrontium-87m. *J Nucl Med* 1: 125, 1960

5. CHARKES ND, SKLAROFF DM, BIERLY J: Detection of metastatic cancer to bone by scintiscanning with ^{87m}Sr. *Amer J Roentgen* 91: 1121–1127, 1964

TABLE 3. PERCENT ^{157}Dy-HEDTA PER LITER OF BLOOD, PERCENT EXCRETED IN URINE, AND HALF-TIMES FOR DISAPPEARANCE FROM BLOOD 3 HR AFTER INTRAVENOUS INJECTION IN HUMANS

			Blood	
Subject	^{157}Dy/liter blood	^{157}Dy in urine	$T_{1/2}$ (min) (fast)	$T_{1/2}$ (min) (slow)
Normal (avg 2)	1.45 ± 0.54	44.5 ± 3.0	13 ± 1	95 ± 2
Abnormal	0.72	37.5	8	64

6. RONAI P, WINCHELL HS, ANGER HO: Skeletal survey for metastatic tumors of bone using ^{18}F and ^{85}Sr with scintillation camera and whole-body scanner. *J Nucl Med* 9, 517–522, 1968

7. FRENCH RJ, MCCREADY VR: The use of ^{18}F for bone scanning. *Brit J Radiol* 40: 655–661, 1967

8. SPENCER R, RAD M, HERBERT R, et al: Bone scanning with ^{85}Sr, ^{87m}Sr, and ^{18}F. *Brit J Radiol* 40: 641–654, 1967

9. WEBER DA, GREENBERG EJ, DIMICK A, et al: Kinetics of radionuclides used for bone studies. *J Nucl Med* 10: 8–17, 1969

10. ANGER HO: Radioisotope Cameras. In *Instrumentation in Nuclear Medicine,* Gerald J. Hine, ed, New York, Academic Press, 1967, pp 485–552

11. ANGER HO: Whole-body scanner Mark II. *J Nucl Med* 7: 331, 1966

12. DURBIN PW, WILLIAMS MH, GEE M, et al: The metabolism of the lanthanons in the rat. USAEC Report, UCRL-3066, 1955

13. O'MARA RE, MCAFEE JG, SUBRAMANIAN G: Rare earth nuclides as potential agents for skeletal imaging. *J Nucl Med* 10: 49–51, 1969

14. YANO Y: Unpublished data, 1970

15. LATIMER R: Personal communications

16. MOGILEVSKAYA OY, RAIKHLIN NT: Rare earth metals. In *Toxicology of the Rare Metals,* Z. I. Izrael'son, ed, Jerusalem, S. Monson, AEC-Tr-6710, 1967, pp 132–141

17. VAN DYKE DC, ANGER HO, PARKER HG, et al: Markedly increased bone blood flow in myelofibrosis. *J Nucl Med* 12: 506–512, 1971