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Thallium-201 for Medical Use. Part 3: Human Distribution and Physical Imaging Properties

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Studies were undertaken to determine the biologic distribution of thallium-201 in man. The disappearance from the blood is extremely rapid and intracellular deposition is nearly immediate. The biologic half-time of thallium was measured by both the Brookhaven whole-body counter and the Donner whole-body scanner, with excellent agreement. The effective whole-body half-time of thallium-201 is about 57 hr. Concentration of activity was seen in the heart, kidneys, large bowel, and thyroid. The whole-body radiation dose is 0.21 rads/mCi.

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The biologic behavior of thallium as a potassium analog and the physical characteristics of thallium-201 have suggested the use of thallium-201 as thallous ion for myocardial imaging (*1,2*). Workers at Brookhaven National Laboratory have developed a method for producing the radionuclide in a form suitable for human use (*2*), and the biologic distribution has been studied in goats (*3*). The results confirm the impression that thallium-201 would be a suitable myocardial imaging agent.

Gamma rays at 167 keV ($D_{1/2}$ in tissue, 4.95 cm) and 135 keV and x-rays at 69–83 keV ($D_{1/2}$ in tissue, 4.15 cm) are available for imaging. Proper instrumentation and collimation are necessary for optimum results.

The studies reported in this communication were instituted in order to compare data obtained in patients with those previously obtained in animals. This is required to confirm dosimetry calculations as well as to determine appropriate imaging times and techniques. The required data include blood levels and the patterns of distribution and excretion for more accurate dosimetry.

METHODS

Tracer, subjects, and sampling. Thallium-201 as thallous chloride was either prepared on the Brookhaven 60-in. cyclotron by a method previously described (*2*) or it was obtained from one of two commercial sources.* No differences in spectrum or biologic behavior were evident in the thallium from the three sources. Eleven patients with a history of coronary artery disease were selected from those on the Hypertension Service, Hospital of the Medical Research Center, Brookhaven National Laboratory. Informed consent was obtained from each. In the initial phase of these experiments, each received 2–5 mCi of thallium-201 intravenously with no special prior preparation. Blood samples were collected at the following intervals after injection: 5, 15, 30, 45, 60, 120, 180 min, and 24 hr. Complete urinary collection was performed over the first 24 hr. Samples were counted in a well counter and compared with an aliquot of a standard, the results being expressed as a percentage of the administered activity. Imaging was performed with a scintillation camera† using the 167-keV gamma photon from thallium-201 or the x-rays from the mercury daughter. Various collimators were used: see *Instrumentation* below and Tables 2 and 3.

Retention studies. Whole-body retention studies were performed on three normal volunteers with the

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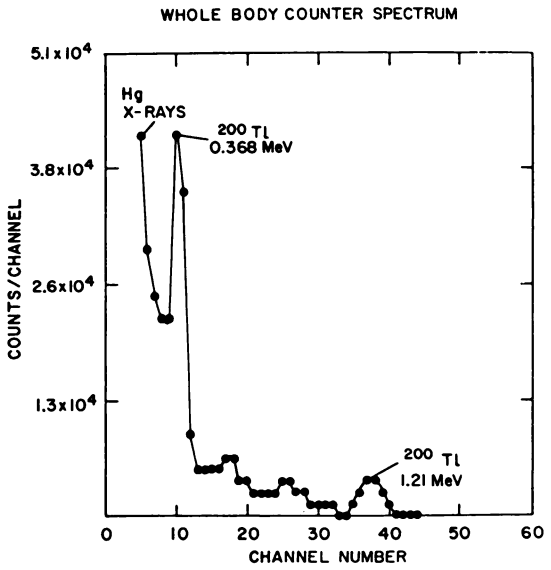

FIG. 1. Spectrum of thallium-200 as determined by Brookhaven National Laboratory whole-body counter. Mercury x-ray peak is not entirely shown because of cut-off by low-level discriminator.

Brookhaven whole-body counter (*4*). For this study, thallium-200 ($t_{1/2}$, 1.04 days) was used because its gamma emission is more abundant and energetic than that of thallium-201; this avoids excessive dead-time losses (from mercury x-rays) and absorption problems. The 0.368- and 1.21-MeV gamma peaks were integrated and counting was performed frequently for 8 days after intravenous injection. Figure 1 shows a typical spectrum from thallium-200 on the whole-body counter. A standard of the injected material was counted each time the three subjects were counted. Counts from the standard were fitted by least squares to a decay curve that gave a half-life of 26.53 hr. The subjects' counts were corrected for this physical decay and the percent retention was obtained as a function of time.

These studies were repeated on the same subjects after potassium loading. Each subject ingested 3 gm of potassium daily in addition to his normal diet, beginning 2 days before injection and continuing through the study period. The additional potassium was in the form of orange juice, tomato juice, and bananas. The study was continued for only 4 days to minimize inconvenience and since any significant change with regard to radiation dose from reduction of whole-body retention would become obvious within this period of time. These data were analyzed as above.

Organ localization. The following procedures were carried out at the Donner Laboratory of the Lawrence Berkeley Laboratory, University of California.

Four millicuries of thallium-201 was injected intravenously into four patients and imaging was performed in multiple projections on an Anger camera for assessment of myocardial uptake. Anterior and posterior supine scans were taken with the whole-body scanner (*5*), which has been digitized to an array of 64 × 384 elements. Regions of interest, such as head, neck and thyroid, heart, kidneys, etc., were flagged with a light pen, and integrated data from these regions were recorded for both the anterior and posterior scans. These data were adjusted by the following procedures:

1. Background from scattered radiation and environment was subtracted, based on background scans done without the patient in place but using the same collimator system and energy window.

2. A second background correction was made for such organs as the heart and kidneys to correct for the over- and underlying tissue contributions. This correction was made by ascertaining the average number of counts per picture element in the region surrounding each organ of interest, and multiplying that by the number of picture elements in the region of interest. The result is subtracted from the region-of-interest total.

3. For such parts as the head, shoulders, heart, etc., the anterior and posterior data were combined by taking the geometric mean (square root of the product).

4. By a method previously described (*6*), the adjusted geometric mean was used to calculate the fraction of administered activity in the body part.

The linear attenuation coefficient μ used for the Hg x-ray window chosen for three patients was 0.16 cm^{-1}. One patient was studied using the gamma photons, for which $\mu = 0.14$ cm^{-1}. The correction was performed on each scan of four patients. The longest followup was 14 days after administration of 4 mCi.

5. Tissue distribution was studied in two dogs 24 hr after administration. The animals were killed and selected tissues assayed for radioactivity.

Instrumentation. Spatial resolution and efficiency for imaging thallium-201 were evaluated with various collimators on (A) the Pho/Gamma III HP scintillation camera; (B) a General Electric Radicamera I; and (C) an Ohio-Nuclear Series 100 camera. Spatial resolution was tested with a multiple line-source filled with thallium-201 and covered by 2 in. of heavy plastic to simulate chest-wall scattering. The image of the line-source was digitized in a 128 × 128 array on a computer system,‡ and a profile perpendicular to the line-sources was analyzed to obtain the full width at half maximum (FWHM).

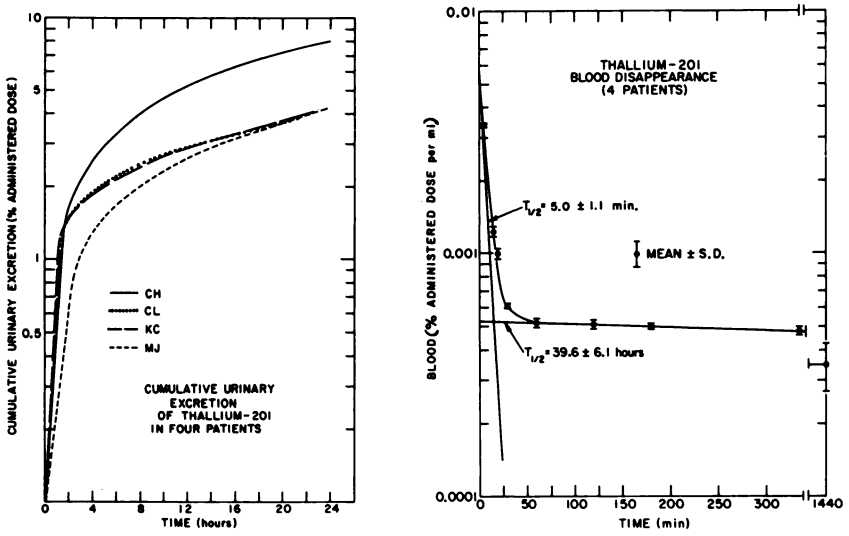

FIG. 2. Cumulative urinary excretion and blood radioactivity levels for first 24 hr after administration of thallium-201 to four patients.

RESULTS

Retention. Blood disappearance was extremely rapid. At 5 min after intravenous administration, only 5–8% of the injected activity remained in the blood, assuming normal blood volumes in these patients. A biexponential disappearance curve was obtained, with 91.5% of the blood radioactivity disappearing with a $T_{1/2}$ of about 5 min. The remainder had a $T_{1/2}$ of about 40 hr (Fig. 2); most of the latter was in the red blood cells during the 24-hr sampling period. The plasma fraction was constant with time in each patient, but among the patients it varied from 28% to 50% of the total blood activity.

Excretion. Little urinary excretion was noted in the first 24 hr, this result being fairly consistent with the whole-body retention studies. Three of the four patients excreted 4% in the first day and the fourth had 8% in the 24-hr urine collection (Fig. 2). Fecal excretion was assumed insignificant on the basis of the whole-body and urine measurements and the measurements of the dog's colon and colon contents.

Myocardial imaging. Myocardial imaging of those patients who underwent blood-clearance studies was carried out from about 5 min after administration up to 24 hr. The myocardial image was still discernible, although fainter than initially, for more than 1 hr after administration. After 4 hr the body showed diffuse generalized radioactivity, with slight accentuation in the gastrointestinal tract and kidneys. Imaging can be performed at any time from 5 min to 1 hr after administration. During this period the blood activity has subsided sufficiently, whereas myocardial activity is essentially constant.

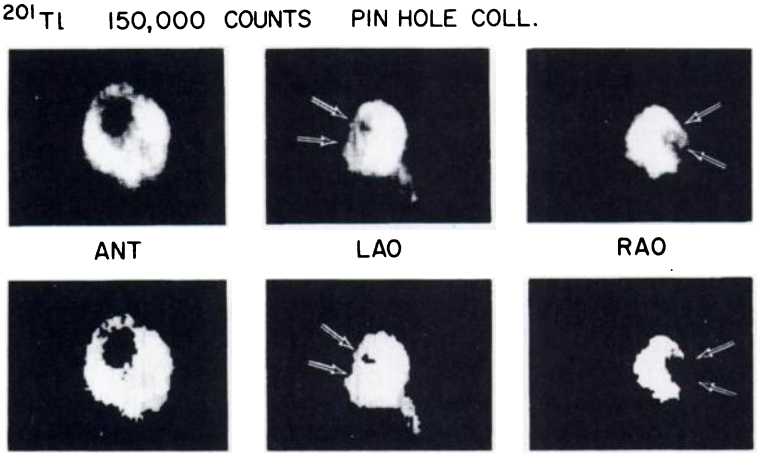

FIG. 3. Thallium-201 images of myocardium, obtained with pinhole collimator, showing perfusion defect of apex of left ventricle and septum. Upper row shows images obtained from 128 × 128 interpolated matrix of computer oscilloscope. In lower images, greater contrast was obtained by digitizing to five-level display; left anterior oblique (LAO) and right anterior oblique (RAO) displays show perfusion defects. Note splenic shadow in LAO.

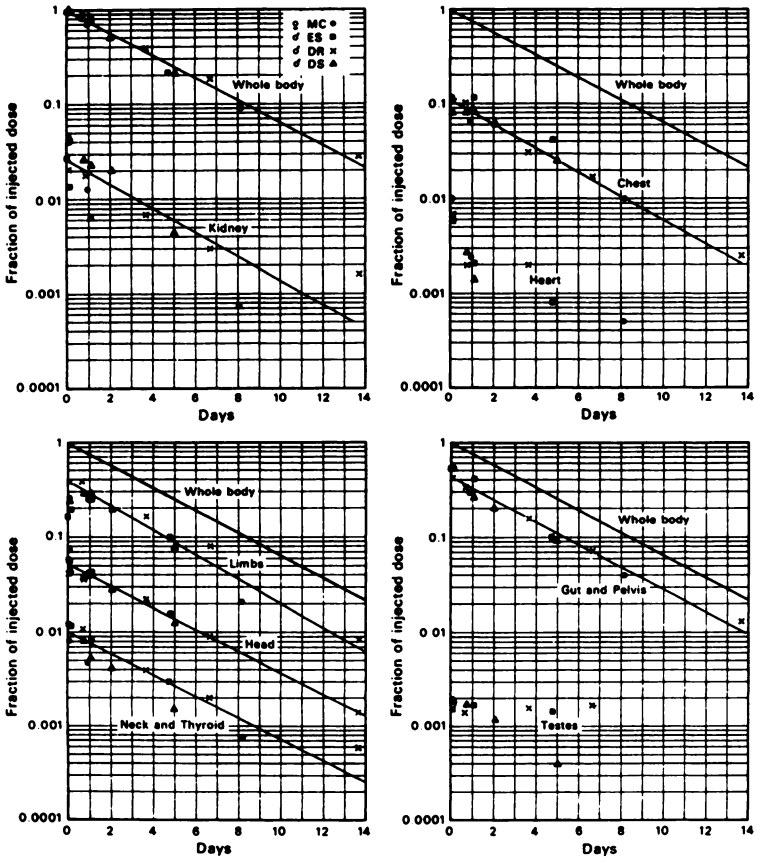

FIG. 4. Whole-body, regional, and organ distribution data for thallium-201 obtained from four patients on the Donner Laboratory whole-body scanner. Patients injected supine.

Count rates over the heart with the 167-keV photons and a high-resolution, low-energy collimator were approximately 200 counts/min-mCi after subtraction of adjacent background radioactivity. Resolution was improved by using a 4.75-mm-aperture pinhole collimator and the more abundant mercury x-rays. The use of a pinhole overcame contrast loss due to the greater scattering at 69–83 keV than at 167 keV. This aspect of the study will be discussed later.

In those patients receiving thallium-201 while fasting and standing, little hepatic concentration of radioactivity was noted. The spleen was visible in the left anterior oblique projection (Fig. 3). This is not surprising considering the relative concentrations found previously in heart and spleen (*3*) and in our dog studies, as well as the anatomic relationships.

Half-time. Whole-body counting of three volunteer subjects using thallium-200 indicated a mean whole-body disappearance half-time of 9.8 days (range, 7.4–12.4 days). The repeat study with potassium loading showed no significant change: the $T_{1/2}$ was 11.0 days (range, 8.1–15.1 days). The amount of potassium loading was small compared with the normal body potassium (~140 gm).

Tissue distribution. Figure 4 shows the sequential distributions of thallium-201 in four patients as determined by the whole-body scanner at Donner Laboratory. Kidney retention was similar to that determined in goats, and the heart concentrations are slightly lower. Late images (Figs. 5 and 6) show persistence of radioactivity in large bowel, kidneys, and testes. There was general agreement among the sequential distribution in all four patients.

The uptake in abdominal organs of two dogs was approximately 20% of the injected dose. Corrected data (*6*) from anterior and posterior whole-body scans of four patients showed about 40% uptake in regions of interest over the lower abdomen and pelvis. The liver uptakes in two dogs were 7.4% and 3.4% of the injected dose after 24 hr. Other studies in dogs indicate that the large-bowel radioactivity is within the muscularis mucosae rather than in the lumen.

About 0.15% of the injected dose is found in the testes of three patients studied. In a 12-kg dog, 0.7%

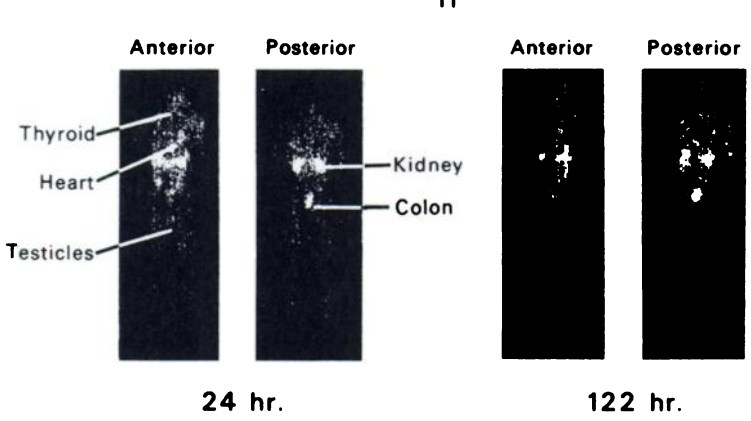

FIG. 5. Whole-body scans showing thallium-201 distribution at 24 and 122 hr after administration. At 24 hr radioactivity is seen in large bowel and kidneys, with faint shadow for myocardium. Relative distribution is not very different at 122 hr. At 162 hr (not shown) distribution is more generalized, but some activity is clearly present in testes.

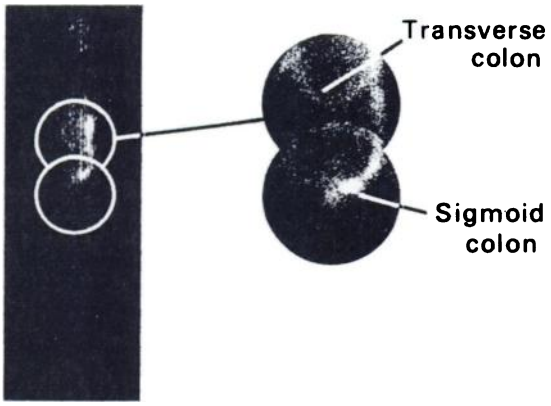

FIG. 6. Large-bowel activity is easily recognized at 8 days after injection of ^{201}Tl.

of the injected activity was found in the 33-gm testes at 24 hr. Studies on a female beagle of the same age showed no appreciable radioactivity in the ovaries. By direct measurement of the ovaries, less than 2 μCi were present after the administration of 1 mCi. The total amount in ovaries and uterus was 0.2% of the injected dose (Table 1). Uptake in the gut and pelvic organs prevented a determination of the uptake in human ovaries.

Thyroid activity was noted in all four of the Donner patients and in one at Brookhaven (Fig. 7), but the net thyroid uptake was determined to be only 0.2% of the injected dose, and the activity disappeared in the first 24 hr.

With the exception of heart and testes, the disappearance curves for the body and its major parts show an effective half-time of 57 hr. Standard aliquots at Donner gave a physical half-life of 74 hr. The whole-body biologic half-time, therefore, approximates the 10 days found in the Brookhaven study, and this is consistent with the urinary excretion data.

Instrumentation. The comparison of three cameras using pinhole, parallel-hole, and converging collimators for detecting the relevant x-rays and gamma

TABLE 1. DISTRIBUTION OF ^{201}Tl IN BEAGLE DOGS (percent injected dose after 24 hr)

Tissue	Male, 11.45 kg	Female, 8.5 kg
Heart	1.7	0.2
Kidneys	4.1	2.6
Gut	1.5	2.7
Lung	0.9	0.9
Spleen	0.3	0.5
Liver	7.4	3.4
Stomach	2.3	2.6
Blood (100 cc)	0.7	0.7
Bladder	0.2	0.2
Whole body	0.3	6.0
Testes	0.7	
Ovaries and uterus		0.2

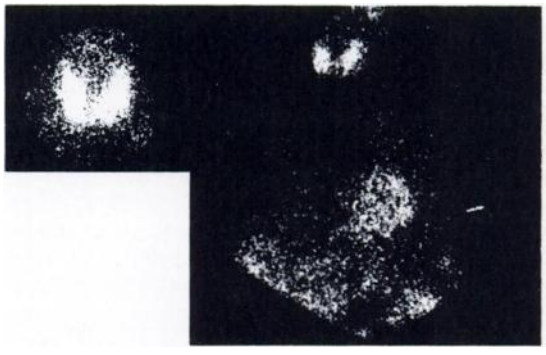

FIG. 7. Considerable concentration of thallium-201 is seen in thyroid of this patient at 1 hr after administration, although there was no history or evidence of thyroid dysfunction. Larger field of view permits comparison between thyroid, myocardium, and lungs.

photons is shown in Tables 2 and 3. Considerable sensitivity is lost when the gamma photons are used rather than the x-rays, because of the 7:1 greater counting rate of the latter despite slightly increased absorption by the overlying chest wall.

The older scintillation cameras (Pho/Gamma III HP and Radicamera I) are not well suited to the imaging of lower-energy photons such as Hg x-rays. The Series-100 camera has an extended energy-range capability with good intrinsic resolution at these low energies. The newer imaging devices now becoming available from several manufacturers will also probably be useful in this energy range. With the newer cameras, the use of straight-bore or converging collimators will increase sensitivity by a factor of 4–10 without significant resolution loss if the Hg x-rays are imaged.

In addition to the organ studies in dogs, we sampled transverse sections of the myocardium at necropsy, from endo- and epicardial surfaces, looking for a thallium concentration gradient. Figure 8 summarizes a study in one dog. There is a 20% increase in the tissue concentration of thallium-201 as one goes from epi- to endocardium. This gradient is similar to that observed for potassium and rubidium (7).

DISCUSSION

In our description of production methods for thallium-201 (2) a comparison of this newer agent with many other myocardial agents was made. We pointed out that all radionuclides currently available for this purpose have at least one major drawback. Positron-emitters such as ^{11}C, ^{13}N, or ^{82}Rb require appropriate imaging devices that are not widely available; they also demand proximity to a cyclotron because of the short half-lives. Other radionuclides are of limted use because of their high-energy emissions (e.g., ^{43}K), limited availability (e.g., ^{129}Cs), or the presence of contaminants (e.g., ^{81}Rb).

Thallium-201 appears to be the most promising agent at this time. While not ideal, the 69–83-keV photons can be used with the newer generation of scintillation cameras with good sensitivity and resolution. Even with the older instruments, a pinhole collimator will provide high resolution, although with reduced sensitivity. The $t_{1/2}$ of 73 hr provides tolerable shelf-life and the possibility of using the radionuclide at some distance from production facilities.

The biologic characteristics are also useful. The rapid clearance of blood radioactivity results in reduced background from the blood pool in the heart. The sustained myocardial retention permits unhur-

TABLE 2. THALLIUM-201 STUDIES ON PHO/GAMMA III HP CAMERA

Collimator	Conditions	Full width at half maximum (mm)	Peak / valley	Contrast = (peak − valley) / valley	Relative* cts/mCi in heart phantom (patients)
4.75-mm pinhole	x-rays, 20% window, scatter	6.5	240/35	5.9	0.69 (0.34)
9.75-mm pinhole	γ-rays, 20% window, scatter	9.5	245/31	6.9	0.32 (0.17)
9.75-mm pinhole	x-rays, 20% window, scatter	12.9	3.43 4.19	2.43 3.19	2.09 (1.0)
9.75-mm pinhole	x-rays, 10% window, scatter	13.3	3.62 4.01	2.62 3.01	1.31 (0.64)
Low-energy high-resolution parallel-hole	γ-rays, 20% window, scatter	12.7	220/99	1.2	0.32 (0.32)
Low-energy Div/Con converging	γ-rays, 20% window, scatter	17.5	85/100	0.85	0.79 (0.43)
Low-energy high-resolution parallel-hole	x-rays, 10% window, scatter	16.0	1.90 1.90	0.90 0.90	(0.75)
Low-energy high-resolution parallel-hole	x-rays, 20% window, scatter	18.7	1.89 2.01	0.89 1.01	(1.2)
Low-energy high-resolution parallel-hole	x-rays, 10% window, no scatter	13.5	3.97 3.35	2.97 2.35	
Low-energy Div/Con converging	x-rays, 20% window, scatter	—	1.67 1.86	0.67 0.86	(3.2)
Low-energy Div/Con converging	x-rays, 10% window, scatter	—	1.92 1.88	0.92 0.88	(1.1)

* Relative to cts/mCi using the ^{201}Tl γ-rays and the high-sensitivity collimator.

TABLE 3. THALLIUM-201 STUDIES ON RADICAMERA

Collimator	Conditions	Full width at half maximum (mm)	Peak / valley	Contrast = (peak — valley) / valley	Relative* cts/mCi
Low-energy parallel-hole	γ-rays, 20% window, scatter	17.8	75/34	1.2	0.184
6-mm pinhole	x-rays, 20% window, scatter	14.1	342/103	2.32	1.16
6-mm pinhole	γ-rays, 20% window, scatter	10.7	65/15	3.3	0.155
Low-energy parallel-hole	x-rays, 20% window, scatter	No contrast obtained			1.32

* Relative to cts/mCi using the ^{201}Tl γ-rays and the high sensitivity parallel-hole collimator.

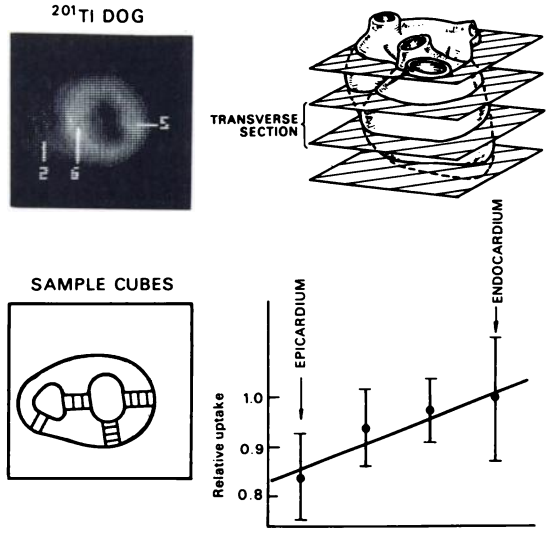

FIG. 8. Autoradiograph of transverse section of heart (upper). Plot shows distribution of activity per unit mass in necropsy slices of dog at 1 hr after injection of thallium-201.

ried imaging. There is adequate concentration in heart muscle to permit gated imaging, thereby improving resolution and allowing evaluation of myocardial contractility.|| The kidney concentration is about 3% of the injected activity and the testicular content is 0.15%. Based on the data obtained in these studies, our estimates of the radiation doses incurred through the administration of 1 mCi of thallium-201 are

Organ	*rads/mCi*
Whole body	0.21
Testes	0.59
Kidney	1.17
Thyroid	1.03
Combined upper and lower large intestines	0.90

The radiation dose to the intestines was calculated by assuming an absorbed fraction of 0.8, based on an assumed combined effective radius of 10 cm for the total mass of the upper and lower large intestines (*8*). This analysis assumes 45% of the injected dose in the large intestines and contiguous structures (liver, kidneys, abdominal musculature) but does not take into account the fact that the radiopharmaceutical appears to concentrate in the muscularis mucosae. The dose estimate is a conservative one.

The other values in the table were calculated using the method of the Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine (*9*).

The long half-life of thallium-201 is a drawback when studies are to be repeated at short intervals, particularly when exercise is used in order to bring out regions of relative ischemia. It may be possible, however, to combine a thallium-201 study with a subsequent study utilizing one of the higher-energy

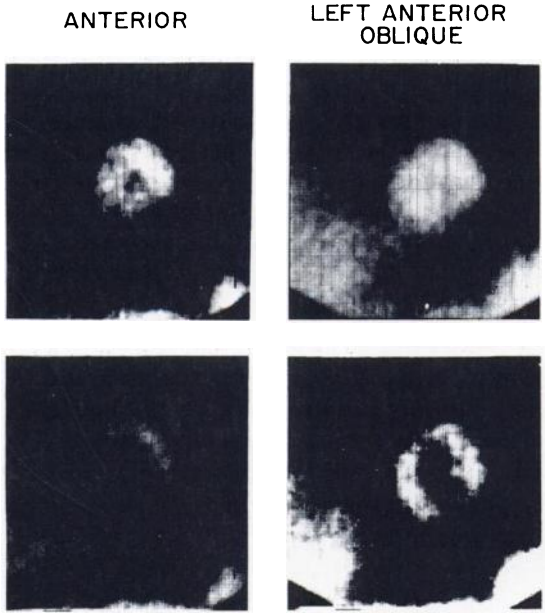

FIG. 9. Gated images following thallium-201 administration, showing left ventricular cavity in systole (top) and diastole (bottom).

photon-emitters. Alternatively, patients under study with a presumptive diagnosis of myocardial ischemia might be examined with thallium-201 only after exercise to emphasize the ischemic regions.

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FOOTNOTES

* New England Nuclear Corp. (North Billerica, Mass.) and Philips-Duphar Co. (Petten, Netherlands).

† Searle Radiographics Pho/Gamma III HP scintillation camera (Des Plaines, Ill.).

‡ General Electric Med II computer.

|| Since the submission of this manuscript we have obtained a converging collimator for use with the Ohio-Nuclear Series-110 large-field-of-view camera. Its improved sensitivity (250,000–350,000 counts per minute) for 2 mCi administered activity (Fig. 9) has permitted gated imaging.

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