Comparison of Technetium-99m-Glucarate and Thallium-201 for the Identification of Acute Myocardial Infarction in Rats

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The scintigraphic identification of acute severe ischemic myocardial injury requires a marker that localizes rapidly and specifically in zones of damaged myocardium. Technetium-99m-glucarate, a six-carbon dicarboxylic acid, which behaves in vivo somewhat like fructose, was recently described as a marker of severe acute ischemic injury with necrosis. This study was performed to determine the interval between the onset of myocardial ischemia and initial uptake and the duration of a positive scan in experimental animals. Serial injections and images were recorded over 10 days following ligation of the left anterior descending coronary artery of the rat. The distribution of ^{99m}Tc-glucarate was compared to that of regional myocardial perfusion monitored with ^{201}Tl. The findings on radionuclide imaging were compared to histologic changes in the myocardium. Sequential pinhole images of both radionuclides were collected at 3 hr, 24 hr, 72 hr and 7–10 days following ligation. Ten rats had normal ^{201}Tl distributions, no uptake of glucarate and no evidence of infarction by TTC staining at autopsy. Twenty-one rats had either ^{201}Tl lesions or evidence of infarction at autopsy. In 17 of these rats, significant acute ^{99m}Tc-glucarate uptake was noted, decreasing at 24 hr, and was not seen at 72 hr or 7–10 days. The extent of perfusion abnormality was greatest at 3 hr in most animals; the lesion decreased in four (33%), increased in one (8%) and remained stable in the remainder. These data suggest that ^{99m}Tc-glucarate may be a useful marker of acute myocardial injury.

J Nucl Med 1992; 33:1988–1993

Differentiating acute severe myocardial injury resulting in necrosis, from ischemia without permanent injury, is important when ruling out infarction in patients with unstable angina. Radionuclide imaging with either ^{111}In-antimyosin Fab (*1–2*) or ^{99m}Tc-pyrophosphate (*3–8*) have been suggested for this purpose, but neither procedure provides data in the critical early hours following onset of chest pain. In the case of antimyosin, an interval of 24 hr between injection and imaging is necessary for blood-pool clearance; in the case of pyrophosphate, injury must be present for at least 6–12 hr before the scan is likely to become positive. Recently, ^{99m}Tc-glucarate, a six-carbon dicarboxylic acid labeled with ^{99m}Tc, was reported as a marker of tissue injury in both cerebral and myocardial infarction (*9–15*). While the mechanism of localization is not fully defined, preliminary studies in cell culture suggest that fructose inhibits the transport of glucarate into renal tubular cells, while glucose had no effect on uptake (*15*). Preliminary studies in rat models of acute severe ischemic injury demonstrated retention of ^{99m}Tc-glucarate in both necrotic and severely ischemic viable tissue (*11–13*), but only a minimally increased uptake in tissue subjected to brief episodes of ischemia.

To determine if imaging with ^{99m}Tc-labeled glucarate could be used to identify acute irreversible injury, we studied rats with acute coronary occlusion. The study was performed to address two issues: First, to determine the temporal relationship of acute ischemic injury to the uptake of ^{99m}Tc-glucarate and second, to determine the relationship of the size and extent of the zone of reduced perfusion to glucarate distribution.

MATERIALS AND METHODS

Animals and Methods

Male 200-g Sprague Dawley rats were anesthetized with pentobarbital (50 mg/kg) administered i.p. Animals were intubated and ventilated on room air with a rodent respirator (Harvard #55-0830). A left thoracotomy was performed at the fourth intercostal space, the pericardium entered and a single fixed ligature placed occluding flow of the left anterior descending (LAD) coronary artery with 6-0 vicryl. The thorax was closed.

Radiopharmaceuticals

Labeling of ^{99m}Tc-glucarate was accomplished by stannous reduction of [^{99m}Tc]pertechnetate in an acid medium in the presence of sodium glucarate. The mixture was incubated for 60 min at room temperature. Radiochemical purity was determined using Whatman No. 1 chromatography paper with a mobile phase of acetonitrile:water (60:40). The ^{99m}Tc-glucarate remained at the origin in the system. Thallium-201 was obtained as sterile

Received March 20, 1992; revision accepted June 11, 1992

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Note: Review of this manuscript was made under the supervision of Guest Editor R.E. Coleman, MD, Duke University, Durham, NC.

pyrogen free thallous chloride (Du Pont Medical Products, Billerica, MA).

Imaging

All radionuclide images were recorded using a large field of view camera equipped with a 3-mm aperture pinhole collimator. The collimator was positioned to view the rats in the anterior projection at a distance of about 15 mm from the chest wall (magnification factor approximately 10×). The data were recorded in a dedicated computer system (Technicare 560, Technicare Solon, OH). Prior to injection of tracer, each rat was reanesthetized with sodium pentobarbital (30 mg/kg). Thallium-201 (300–500 μCi) was administered intravenously and anterior myocardial images were recorded 10 min later with the camera peaked at the 80 keV x-ray with a 20% window. At the conclusion of thallium imaging, 3.5–4.5 mCi of ^{99m}Tc-glucarate was administered intravenously without moving the animal and 50 min later the camera was repeaked to image the 140 keV photon of ^{99m}Tc with a 20% window. The animals were injected and imaged in this fashion at 3 hr, 24 hr, 72 hr and 7–10 days following ligation of the LAD.

Postmortem Myocardial Study

At the end of the experiment, the rats were killed with an overdose of ether. The heart was removed and divided into four slices from base to apex. These slices were stained with a 2,3,5 triphenyltetrazolium chloride (TTC, Sigma) at 37°C for 20 min. A tracing of each slice was made depicting the TTC staining patterns. The specimens were fixed in 10% neutral buffered formalin and embedded in plastic blocks (*16*). Sections of 4-μm thickness were prepared from the short axis of the midventricular level and stained with hematoxylin-eosin (H & E). The lesions identified by imaging were correlated with the TTC stained specimens and light microscopy.

Interpretation of Images

The myocardial uptake of ^{99m}Tc-glucarate was evaluated semiquantitatively by blinded observers. The images were scored as follows: 0 = no myocardial uptake or faint uptake (< liver or bone uptake), 1 = mild myocardial uptake (= liver or bone uptake), 2 = moderate myocardial uptake, 3 = severe myocardial uptake. A score of 1 or greater was considered positive.

The initial myocardial perfusion images of ^{201}Tl were evaluated as follows: 0 = no myocardial defects (including slight decreased uptake of apex), 1 = myocardial defect less than 20% of left ventricular myocardium in the anterior view, 2 = myocardial defect from 20% to 40%, 3 = myocardial defect greater than 40%.

Interpretation of Postmortem Studies

To confirm the region of myocardial injury following surgery, both postmortem myocardial TTC staining and histopathological studies were employed. Two criteria were used for the macroscopic detection of infarction: Absence of TTC staining (white color) in a zone and visible regional myocardial thinning. The extent of myocardial infarction was determined as follows: small = unstained or thinning in a region less than 10% of left ventricular myocardium in the two central slices; medium = unstained or thinning extending over a region of 10% to 25% in either of the two central slices and large = unstained or thinning in a region greater than 25% in both of the two central slices. Fibrosis of the myocardium was scored using light microscopy as: 0 = no fibrosis; 1 = fibrosis less than 50% of transmural myocardium; 2 = fibrosis from 50% to 80% and 3 = fibrosis greater than 80%.

RESULTS

Histological Findings

Of the 31 rats surviving acute open chest myocardial ligature placement, 21 rats sustained varying degrees of myocardial damage, as revealed by postmortem examination, while 10 had no myocardial necrosis (Table 1). Within one day of surgery, seven rats (Animals 13–17, 20–21) that had undergone imaging at 3 hr died (all were scan positive); histologic examination of their hearts revealed evidence of early myocardial infarction, manifested by thinning and wavy myocardial fibers, necrotic fibers with contraction bands at the periphery of the infarct, interstitial edema and infiltration of inflammatory cells, but no fibrous changes (Fig. 1). In three additional animals with infarction that died between 3 and 5 days, additional histological changes of early fibrosis were observed. At 7–10 days obvious changes of fibrosis were observed (Fig. 2).

Myocardial Perfusion as an Indicator of Myocardial Injury

Of the 21 rats with myocardial damage, images at 3 hr were abnormal in 19 rats, while scans in 2 rats were negative. One of the two perfusion-negative rats developed a positive scan by 24 hr (Table 1). The remaining rat died following negative perfusion scans at 3 and 24 hr; TTC staining and light microscopy confirmed the presence of a small zone of myocardial necrosis. Of the 14 rats with perfusion abnormalities seen at 3 and 24 hr who survived to 72 hr, the extent of the perfusion abnormality matched the macroscopic extent of infarction. In one rat (Animal 9) with subendocardial infarction, the thallium scan underestimated the extent of necrosis. None of the 10 rats with normal postmortem exams were thallium scan positive at any time. In this model, the thallium scan had a 90% (19 of 21) sensitivity for identification of infarction at 3 hr, 94% (16 of 17) at 24 hr, 93% (13 of 14) at 72 hr and 92% (11 of 12) at 5–10 days. No false-positives (0 of 10) were observed.

In the 12 rats with myocardial damage observed consecutively over 5–10 days, the extent of the perfusion defect size at the end of the study changed from that seen acutely in five animals. The extent of perfusion reduction was maximal acutely, and decreased in four (33%), increased in one (8%) and remained stable in 58% (Table 2).

Technetium-99m Glucarate

Acute (3 hr). Of the 21 rats with histologic evidence of infarction, 17 were positive (18%). When compared to the 19 animals with abnormal perfusion scans acutely, 17 were ^{99m}Tc-glucarate positive (Table 3 and Figs. 3 and 4) (89%). The scans in the remaining two rats (Animals 18 and 19) were uninterpretable due to unusually delayed clearance from the blood pool. Of the 12 rats with negative glucarate scans, none became positive on subsequent images.

TABLE 1
Summary of ^{201}Tl and ^{99m}Tc-Glucarate Image Data Following LAD Ligation in Rats

No.	3 hr		24 hr		72 hr		7–10 days		Days of sacrifice	Macro/TTC size of infarction	Histology fibrosis
	Tl	Tc-G	Tl	Tc-G	Tl	Tc-G	Tl	Tc-G			
1	3	3+	2	2+	2	0	2	0	7 d	large	2
2	3	3+	3	1+	3	0	3	0	9 d	large	3
3	3	3+	3	1+	3	0	3	0	10 d	large	3
4	2	3+	2	1+	2	0	2	0	10 d	medium	2
5	1	3+	2	1+	2	0	2	0	8 d	medium	3
6	3	3+	2	0	2	0	2	0	8 d	medium	3
7	3	3+	1	0	1	0	2	0	9 d	medium	3
8	2	2+	2	1+	2	0	2	0	8 d	medium	3
9	2	2+	1	1+	0	0	0	0	9 d	normal	1
10	1	1+	1	0	1	0	1	0	8 d	small	3
11	3	2+	2	1+	2	0			3 d†	medium	—
12	1	2+	1	0	1	0			3 d	small	2
13	2	2+	2						24 hr†	medium	0
14	3	3+							14 hr*	large	0
15	3	2+							16 hr*	large	0
16	3	2+							17 hr*	large	0
17	3	1+							10 hr*	large	0
18	3	B.P.	3	2+	3	0	3	0	10 d	large	3
19	3	B.P.	3	1+	3	0	3		5 d†	large	2
20	0	0	2						30 hr†	medium	0
21	0	0	0	0					28 hr†	small	0
22	0	0	0	0	0	0	0	0	7 d	normal	normal
23	0	0	0	0	0	0	0	0	9 d	normal	normal
24	0	0	0	0	0	0	0	0	9 d	normal	normal
25	0	0	0	0	0	0	0	0	9 d	normal	normal
26	0	0	0	0	0	0	0	0	10 d	normal	normal
27	0	0	0	0	0	0	0		10 d†	normal	normal
28	0	0	0	0	0	0			3 d	normal	normal
29	0	0	0	0	0				3 d†	normal	normal
30	0	0	0	0					24 hr	normal	normal
31	0	0	0						24 hr†	normal	normal

* Probable myocardial damage death.
† Probable anesthesia death.
Tl = ^{201}Tl; Tc-G = ^{99m}Tc-glucarate; macro/TTC = macroscopic and TTC stain findings; B.P. = blood-pool image.

Subacute (24 hr). Only 12 of the 17 rats with perfusion defects that were ^{99m}Tc-glucarate positive at 3 hr survived to be reinjected at 24 hr. Of these 12 animals, 8 rats remained glucarate positive and 4 rats developed no uptake on their 24-hr images (Table 3). The two animals with positive thallium scans and blood pool on their acute glucarate images had positive glucarate scans when reinjected at 24 hr; their thallium scans remained abnormal. Of the 12 rats which were both perfusion and acutely glucarate negative, 10 rats remained glucarate negative at 24 hr. Two additional rats died before their glucarate scan at 24 hr.

Subchronic (72 hr). All glucarate scans at 72 hr were negative. The eight rats that were glucarate positive at 24 hr did not have focal myocardial localization on their 72-hr images. The perfusion scans were acutely positive in all eight and remained positive in seven. The perfusion abnormality in the four rats whose glucarate scans turned from positive to negative at 24 hr did not change (Table 3).

Chronic (7–10 days). No rats were glucarate positive at 7–10 days after ligation.

DISCUSSION

The study was performed by ligating the LAD coronary artery of anesthetized rats. Since the heart rate of the rat is about 400 bpm, it is difficult to precisely place the ligature. As a result, the ligation procedure results in occlusion of the LAD in about two-thirds of the animals, while producing no ischemia in the remainder. This phenomenon allows all animals to be subjected to the same experimental protocol, but provides a control group that is identified by histopathology at the completion of the study.

Under circumstances of fixed occlusion of the LAD, ^{99m}Tc-glucarate concentrates in the areas of acute injury. Concentration in the area of the injury was maximal in most animals at about 3 hr, faded by 1 day and was no longer visible by 3 days. These findings suggest ^{99m}Tc-

FIGURE 1. Representative photomicrography (320×) at 30 hr after LAD artery ligation. Necrotic fibers with contraction bands and calcium deposition are seen.

glucarate may be useful to identify acute severe injury early, within hours of onset. Orlandi et al. (*14*) reported similar findings in an occlusion reperfusion model in the dog. In that study, myocardial glucarate uptake was higher in dogs imaged within hours of release of a 90-min occlusion than those imaged at 2 days.

Preliminary studies suggested that ^{99m}Tc-glucarate is retained in both necrotic and severely ischemic but viable tissues (*11–13*). In relatively mild ischemia caused by transient occlusion of the coronary artery in the dog, however, Orlandi (*14*) did not identify glucarate uptake. This finding could be explained by the observation that ischemic tissue-to-blood ratios of glucarate only exceeded 1 in regions with acute severe ischemia, even though the ischemic-to-normal tissue ratio exceeded 1 in regions with

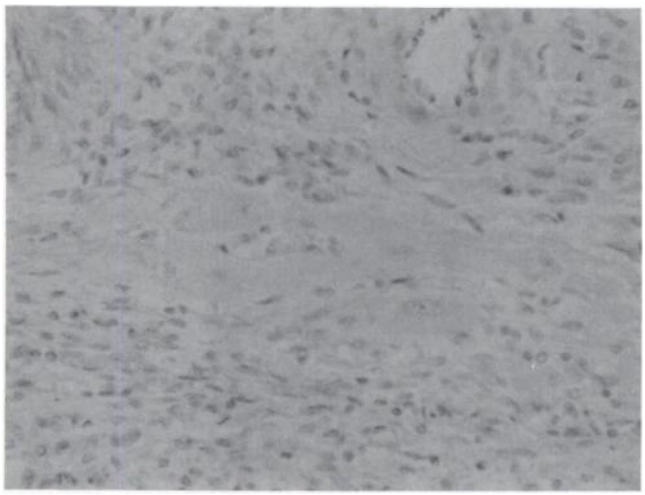

FIGURE 2. Representative photomicrography (320×) at 7 days after LAD artery ligation. Fibrous changes with replacement of myocytes by fibroblasts and collagen fibers are apparent.

TABLE 2
Thallium-201 Defect Size Following LAD Ligation Relative to 3 Hr in Rats with Myocardial Infarction

3 Hr	24 Hr	72 Hr	5–10 Day		
12			1	Increased	1
			7	No change	7
			4	Decreased	4

mild ischemia (Yaoita et al., unpublished data). In the present study, all rats with normal perfusion on their ^{201}Tl images had no significant uptake of glucarate. Even in two rats with histologic evidence of acute myocardial injury but normal perfusion scans, no significant glucarate uptake was observed. This may have been due to the relatively small size of the lesion in these animals. On the other hand, in one rat with subendocardial infarction, the extent of glucarate uptake was larger than that of the thallium perfusion defect seen acutely.

These data suggest that ^{99m}Tc-glucarate uptake identifies acute necrotic myocardium. While the mechanism of ^{99m}Tc-glucarate accumulation is unknown, previous studies in cell culture by Yaoita et al. suggest that glucarate may serve as an analog of fructose (*15*). In rabbits undergoing an occlusion/reperfusion study, the pattern of ^{99m}Tc-glucarate accumulation was different than that of ^{3}H-deoxyglucose (Yaoita et al., unpublished data).

Technetium-99m-pyrophosphate uptake occurs within 10–12 hr of the onset of infarction due to permanent coronary occlusion and increases in intensity over 24–72 hr (*3–5*). Under circumstances of reperfusion, uptake of pyrophosphate occurs within a few hours of the event (*6–7*). Our data suggest that ^{99m}Tc-glucarate may permit earlier detection of acute myocardial infarction, since uptake was observed within 2 hr in animals with persistent LAD ligation.

Technetium-99m-glucarate has other potential advantages for the detection of acute necrosis: Blood clearance is rapid, and is primarily through the urine (*14*), and there is no interference from overlying ribs (uptake in the spine is usually seen). The images we recorded within 1 hr of injection of ^{99m}Tc-glucarate were generally interpretable as negative or positive, although two animals with very large

TABLE 3
Technetium-99m-Glucarate Images in Rats with Myocardial Infarction

	3 Hr	24 Hr	72 Hr	7–10 Days
Positive	17	→ 8		
Negative		→ 4	→ 12	→ 10
(Died)		(5)	(0)	(2)

Except for two rats with unusually delayed blood pool and another two rats with myocardial infarction but normal perfusion image at 3 hr.

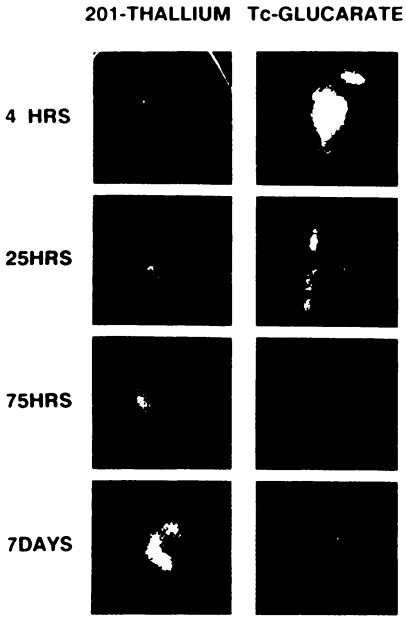

FIGURE 3. Serial ^{201}Tl (left) and ^{99m}Tc-glucarate images (right) in a rat with a large myocardial infarction (histologic findings from Day 7 shown in Fig. 2). The thallium images show a persistent perfusion defect, beginning immediately after ligation, and continuing unchanged through Day 7. The glucarate images demonstrate maximal myocardial uptake at 4 hr, decreasing by 25 hr and no uptake at 75 hr and 7 days. The slight uptake seen above and to the left of the myocardium is in the thoracotomy scar. The vertical structure is the spine, which is usually seen to some degree on glucarate rat images.

thallium lesions that had focal uptake on their 24-hr studies appeared to have blood-pool uptake on their 3-hr studies.

Indium-111-antimyosin antibodies are another useful imaging agent for detecting myocardial infarction (*1–2*).

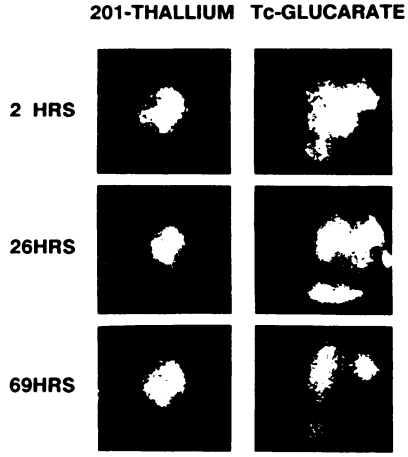

FIGURE 4. Serial ^{201}Tl images (left) and ^{99m}Tc-glucarate images (right) in a rat with a small infarct (#12 in Table 1). The thallium images demonstrate an apical lesion beginning immediately after ligation, while the glucarate images depict definite myocardial uptake only at 2 hr. Uptake in the thoracotomy scar and spine is also seen.

While the uptake of ^{111}In-antimyosin is due to specific antigen-antibody interaction, this agent has the disadvantage of relatively slow blood-pool clearance, which precludes imaging for about 24 hr after injection in most patients with small areas of myocyte necrosis.

Another approach to the scintigraphic detection of acute myocardial necrosis utilized ^{99m}Tc-glucoheptonate. This technique, first described by Rossman et al. (*17–18*), identified early localization of this seven-carbon dicarboxylic acid at sites of acute myocardial necrosis. When these studies were extended to man by Roberts et al. (*19*) and Alonso et al. (*20*), the rapid uptake was confirmed, but the contrast between the lesion and background proved too limited for reliable clinical use.

Our animal model of myocardial infarction was designed to assess whether the uptake of ^{99m}Tc-glucarate would be useful in the situation of no coronary reflow; a circumstance where most investigators have observed the lowest concentration of infarct avid radiopharmaceuticals in the early hours of injury and necrosis. Although further evaluation of this characteristic of ^{99m}Tc-glucarate both in relevant experimental animal models and humans will be required to determine its clinical utility, the preliminary results observed in these experiments suggest that high contrast images can be obtained within 1 hr of injection and 3 hr of onset of injury. Delaying the time of injection to 24 hr or beyond, however, may result in false-negative images.

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SELF-STUDY TEST

11. Legg-Perthes disease
12. Septic arthritis
13. Hemarthrosis
14. Gaucher's disease
15, Transient synovitis of the hip
16. Chondroblastoma

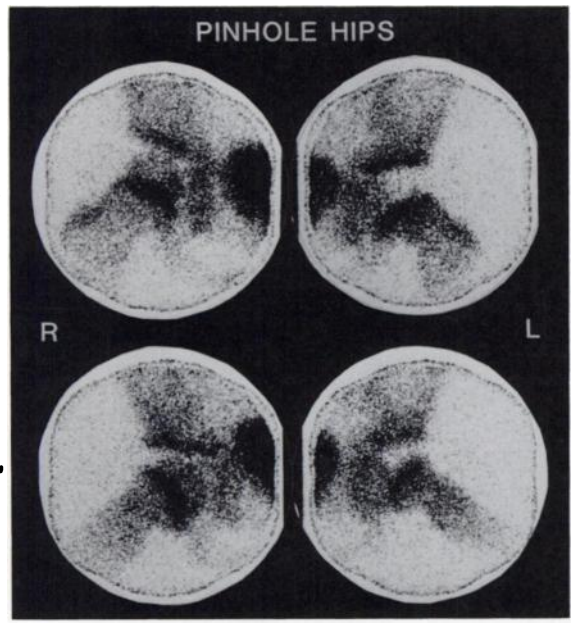

FIGURE 3.

Figure 4 shows ^{99m}Tc MDP images obtained 3 and 24 hours postinjection. The abnormality noted could be caused by

17. radiation therapy.
18. focal calyceal obstruction.
19. renal cell carcinoma.
20. sickle cell anemia.
21. metastatic osteogenic sarcoma.

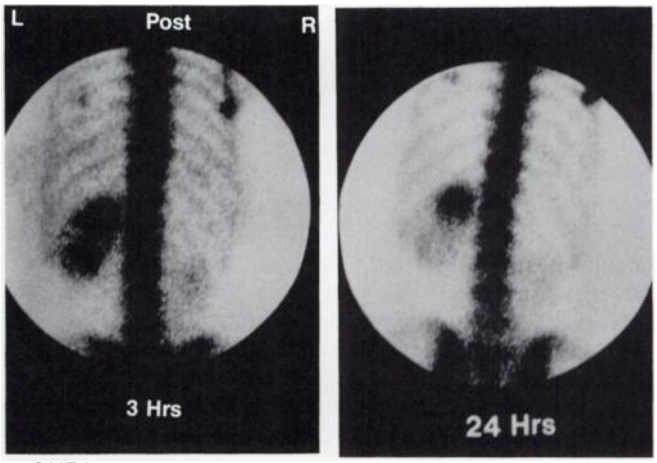

FIGURE 4

SELF-STUDY TEST
Skeletal Nuclear Medicine
ANSWERS

ITEMS 1–5: Hepatic Activity on Bone Scintigraphy
ANSWERS: 1, F; 2, T; 3, T; 4, F; 5, F
The images in Figure 1 demonstrate increased hepatic uptake of the radiopharmaceutical. Hepatic uptake on bone scintigraphy occasionally results from the formation of a colloid of technetium oxides (e.g., TcO_2), which may occur when the pH of the reaction mixture is alkaline rather than acidic, and when excessive stannous ion is present. On radiochromatography, this colloidal contaminant will be measured as "free reduced technetium," which remains at the origin on paper or thin-layer chromatograms in either saline or acetone. Aluminum ion breakthrough in the eluate of a technetium generator may result in colloid formation through production of an aluminum-technetium complex. This effect begins to appear at Al^{+3} concentrations in the eluate exceeding 10 μg/ml. This aluminum effect also has been observed in patients taking aluminum-containing antacids, and presumably reflects colloid formation in vivo. The reticuloendothelial system of the liver is quite efficient in phagocytizing ^{99m}Tc colloids, whatever the origin.

The inadvertent introduction of oxygen or other oxidizing agents into the reagent vial will lead to reoxidation (or insufficient reduction) of

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