COMPARISON OF ^{99m}Tc COMPLEXES FOR RENAL IMAGING

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The distribution of 17 different agents for renal imaging was compared in the rabbit by organ radioassay at 1 hr. Similarly, ^{99m}Tc complexes of iron-ascorbate, glucoheptonate (GHA) and 2,3-dimercaptosuccinic acid (DMS), and ^{203}Hg-chlormerodrin were compared in the dog. The distribution of ^{99m}Tc-GHA and DMS was assessed in the human by blood and urinary clearance, external renal measurements, and scintillation camera imaging, and compared with older renal radiopharmaceuticals. Radiation dose estimates, based chiefly on human data, were calculated. Technetium-99m-DMS reaches a high concentration in the renal cortex and its urinary excretion rate and blood clearance are slow. It is excellent for imaging the renal parenchyma without activity in pelvocalyceal collecting system. However, it readily oxidizes and must be used within 30 min of preparation. The biologic distribution of ^{99m}Tc-GHA is similar to gluconate and iron-ascorbate complex. Its renal concentration is not as great as that of DMS but its blood and urinary clearances are much faster, resulting in lower radiation doses to most organs. Early camera images with this agent usually demonstrate both the renal parenchyma and collecting system. In later images, there is excellent demonstration of the parenchyma alone, superior to that obtained with ^{99m}Tc-Sn-DTPA. It is a very stable complex and may be used for at least 5 hr after preparation. All radioactive renal agents examined to date have a significant concentration in the liver, making an accurate quantitative comparison between the two kidneys difficult.

Since Harper's initial report (*1*) on 6-hr ^{99m}Tc as a tracer in biology and medicine in 1962, this radionuclide has been incorporated into many complexes for imaging various organs because its physical characteristics are excellent for scintillation detectors (*2,3*). Harper and Lathrop (*4*) developed an iron-ascorbate complex of ^{99m}Tc that localized in the kidney sufficiently to obtain good radioisotopic images of this organ. Since then, a great number of different technetium preparations have been developed for this purpose, including complexes of EDTA (*5*), DTPA (*6,7*), mannitol (*8*) [with and without gelatin (*9*)], penicillamine-acetazolamide (*10,11*), caseidin (*12*), and tetracycline (*13*). Technetium-99m (V)-citrate (*14*) and ^{99m}Tc-Sn DTPA (*15*) have been proposed for measurement of the glomerular filtration rate. The technetium complex of gluconate was first described by Charamza and Budikova (*16*) in 1969 and was later prepared electrolytically as a freeze-dried kit containing stannous ions (*17*); subsequently, this became a popular renal scanning agent, particularly in Australia (*18*). More recently, ^{99m}Tc-glucoheptonate (GHA) (Fig. 1) was developed

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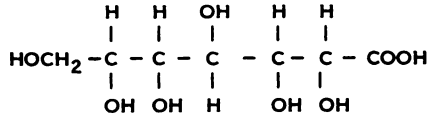
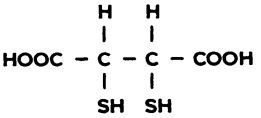


GHA (MW 226)



DMS (MW 182)

FIG. 1. Chemical structure of glucoheptonate (GHA, glucose carboxylic acid) and 2,3-dimercaptosuccinic acid (DMS).

by Adler, Camin, and Gold of the New England Nuclear Corp. and 2,3-dimercaptosuccinic acid (DMS; MPI kidney "Scintigraphin Reagent") (Fig. 1) and other mercaptocarboxylates labeled with ^{99m}Tc were developed as renal radiopharmaceuticals by Lin, Khentigan, and Winchell of the Medi-Physics Corp. (*19*).

With such a variety of ^{99m}Tc renal agents, the selection of one or two most suitable for clinical application has become difficult. The present work summarizes an intercomparison of the most promising ^{99m}Tc renal imaging agents in experimental animals and man.

MATERIALS AND METHODS

All chemicals used in this study were of either analytical or USP grade, obtained from commercial sources* and used without any further purification. Mercury-203-chlormerodrin was obtained commercially (E. R. Squibb & Co., New Brunswick, N.J.) also. Both lysozyme and ribonuclease were labeled with ^{131}I by an iodine monochloride method (*20*) and contained 30–60 mg protein per microcurie. Free iodide in these labeled compounds was less than 2% as determined by paper chromatography using Whatman No. 1 paper and 85% methanol in water as the solvent.

Indium-114m was obtained as chloride (ICN, Cleveland, Ohio) and the DTPA complex was prepared by mixing 100 mg DTPA (pentasodium salt) with the indium solution and adjusting the pH to 7.0 with dilute sodium hydroxide. This solution contained carrier indium to the extent of 3 mg/mCi. Unbound ^{114m}In in the DTPA complex was negligible as determined by paper electrophoresis using barbital buffer (pH 8.5) (Beckman electrophoresis unit). The complex moved away from the origin while the unbound indium stayed at the origin.

The pertechnetate used in these studies was obtained from a commercial ^{99m}Tc generator (New England Nuclear Corp.). Technetium-99m-albumin was prepared by the method of McAfee, et al (*21*) and contained less than 5% free pertechnetate as measured by paper chromatography. Technetium-99m-inulin was prepared by the stannous chloride method of Subramanian (*8*) and ^{99m}Tc-caseidin by the method described by Winchell (*12*). The iron ascorbic acid compound was prepared using a method similar to that for albumin labeling but omitting the albumin. The final pH was 6.5 and the free pertechnetate level was negligible. The "iron ascorbic acid DTPA" compound (Renotec) was prepared from a commercial kit (E. R. Squibb & Co.). The ^{99m}Tc DMS preparation also was made from a commercial kit containing 0.547 mg DMS and 0.19 mg stannous chloride per milliliter at pH 2–3 (Mediphysics, Inc., Kidney Scintigraphin™ Reagent).

All other ^{99m}Tc compounds listed in Table 1 [DTPA, calcein blue, mannitol, gluconate, glucoheptonate (also available from New England Nuclear Corp.), and lactobionate] were prepared from freeze-dried kits. These stannous chelates were made by mixing 100–200 mg of the compound in aqueous solution with 100–200 μg of freshly prepared stannous chloride in dilute HCl in a total volume of 4 ml. Subsequently, the vials were freeze-dried under sterile conditions. The calcein blue kit contained 50 mg of this compound and 100 μg of stannous chloride. For labeling, ^{99m}Tc as obtained from the generator was added to the freeze-dried kits in a maximum volume of 5 ml. The labeling yield was quantitatively high and the free pertechnetate levels were less than 2% as determined by paper chromatography in 85% methanol.

Organ distribution studies of these radioactive renal agents were performed in adult albino New Zealand rabbits weighing 2.5–4.0 kg. Injections of 5–10 μCi of the long-lived compounds (^{203}Hg, ^{131}I, ^{114m}In) and about 50 μCi of ^{99m}Tc complexes were made through a marginal ear vein. For the ^{131}I protein compounds, lysozyme and ribonuclease, 100–500 μg/kg of carrier protein were administered. For ^{99m}Tc-caseidin, the dose ranged from 1 to 5 mg/kg body weight. The ^{114m}In-DTPA compound contained 50–60 μg carrier indium per kilogram body weight. The animals were sacrificed 1 hr after administration of the compounds. Blood was sampled from the heart and the liver was removed and weighed. One whole kidney and samples from the cortex and medulla were counted along with samples of other organs in a scintillation well counter and compared with a standard. Urine was collected in toto from the bladder and aliquots were counted in the well counter. For calculation purposes, the total blood was assumed to be 7% and muscle 43% of the body weight. The distribution of ^{99m}Tc-glucoheptonate and ^{99m}Tc-DMS was studied at 15 min, 3, 6, and 24 hr after administration of the compound in addition to the 1-hr time interval.

Organ distribution was determined in adult mongrel dogs weighing 20–25 kg after intravenous injection of 200–250 μCi of the ^{99m}Tc complexes and 10–15 μCi of ^{203}Hg-chlormerodrin. After sacrifice at 1 hr, the dose in blood, muscle, liver, whole kidney, kidney cortex, and medulla was determined by

* Sigma Chemical Co., St. Louis, Mo.; Pfaltz & Bauer, Flushing, N.Y.; lysozyme and ribonuclease obtained from Miles Laboratories; and caseidin was kindly supplied by Saul Winchell, Medi-Physics, Inc., Emeryville, Calif.

TABLE 1. ONE-HOUR DISTRIBUTION OF RENAL AGENTS IN RABBITS

	Percent dose in whole organ					Ratios*			
	Two kidneys	Blood	Liver	Muscle	Urine	Kidney/ blood	Kidney/ liver	Kidney/ muscle	Cortex/ medulla
^{203}Hg-chlormerodrin (18)†	52.0 ± 6.10	4.3 ± 1.00	5.2 ± 1.80	3.7 ± 0.87	16.0 ± 4.3	165.0 ± 63.00	60.0 ± 29.00	1158 ± 353.0	5.60 ± 2.60
^{131}I-lysozyme (3)	22.0 ± 3.70	15.0 ± 1.00	3.8 ± 0.70	18.0 ± 2.10	2.4 ± 1.9	18.0 ± 4.90	32.0 ± 14.00	93 ± 25.0	9.60 ± 4.40
^{131}I-RNASE (3)	16.0 ± 5.70	20.0 ± 5.10	2.9 ± 1.30	21.0 ± 2.70	10.0 ± 3.1	13.0 ± 6.30	34.0 ± 16.00	73 ± 30.0	5.70 ± 4.20
^{114m}In-DTPA (6)	2.7	7.7	1.1	6.0	51.0	4.3	12.0	59	1.50
^{99m}TcO$_4$ (3)	2.2 ± 0.19	16.0 ± 1.60	7.0 ± 1.80	10.0 ± 2.70	19.0 ± 11.0	1.4 ± 0.07	1.7 ± 0.27	14 ± 2.9	0.41 ± 0.08
^{99m}Tc-calcein blue (3)	2.9 ± 0.55	8.9 ± 2.70	3.5 ± 0.59	3.8 ± 1.40	58.0 ± 2.5	4.8 ± 2.10	5.6 ± 2.00	70 ± 34.0	1.50 ± 0.29
^{99m}Tc-Sn-DTPA (3)	3.4 ± 0.25	8.6 ± 1.10	1.9 ± 0.48	5.4 ± 0.85	53.0 ± 2.8	4.6 ± 0.05	14.0 ± 1.80	45 ± 3.3	1.40 ± 0.14
^{99m}Tc-albumin (3)	8.4 ± 1.20	59.0 ± 6.40	9.3 ± 3.70	6.8 ± 1.20	22.0 ± 1.5	1.6 ± 0.28	5.4 ± 1.60	87 ± 6.4	1.60 ± 0.30
^{99m}Tc-Renotec (3)	12.0 ± 2.20	5.5 ± 0.81	2.2 ± 0.79	3.9 ± 1.40		22.0 ± 3.80	33.0 ± 12.00	199 ± 64.0	3.00 ± 0.60
^{99m}Tc-gluconate (6)	13.0 ± 2.70	4.4 ± 0.70	1.8 ± 0.52	2.7 ± 0.36	59.0 ± 7.0	33.0 ± 8.50	40.0 ± 7.20	336 ± 76.0	9.70 ± 4.60
^{99m}Tc-glucoheptonate (6)	13.0 ± 2.70	4.0 ± 1.20	1.5 ± 0.41	3.2 ± 1.50	61.0 ± 9.0	42.0 ± 10.00	71.0 ± 23.00	357 ± 145.0	5.00 ± 1.40
^{99m}Tc-Fe-ascorbate (6)	15.0 ± 2.30	7.3 ± 1.40	3.7 ± 1.70	6.7 ± 1.80		24.0 ± 3.80	34.0 ± 1.70	162 ± 31.0	3.50 ± 1.40
^{99m}Tc-inulin (6)	15.0 ± 3.90	6.6 ± 0.90	5.7 ± 1.40	4.4 ± 0.83	49.0 ± 9.7	25.0 ± 5.60	14.0 ± 4.90	226 ± 43.0	2.80 ± 0.83
^{99m}Tc-mannitol (6)	15.0 ± 3.10	4.5 ± 0.45	1.5 ± 0.41	3.0 ± 0.29	57.0 ± 5.0	40.0 ± 12.00	57.0 ± 37.00	367 ± 120.0	5.10 ± 1.90
^{99m}Tc-lactobionate (6)	18.0 ± 3.80	4.6 ± 1.10	1.3 ± 0.20	2.6 ± 0.63	60.0 ± 6.8	46.0 ± 8.80	88.0 ± 32.00	496 ± 108.0	7.80 ± 2.00
^{99m}Tc-DMS (6)	20.0 ± 4.00	17.0 ± 1.90	3.2 ± 0.49	9.8 ± 2.20	15.0 ± 5.2	18.0 ± 4.40	46.0 ± 12.00	197 ± 74.0	17.00 ± 4.20
^{99m}Tc-caseidin (27)	24.0 ± 4.50	15.0 ± 3.30	5.2 ± 1.70	5.1 ± 0.84	36.0 ± 6.7	22.0 ± 6.50	32.0 ± 14.00	398 ± 136.0	6.80 ± 2.50

* Ratios derived from percent dose/1% body weight.
† Indicates number of animals for each agent.

counting multiple samples in a well scintillation counter in comparison with a standard. Again, blood was assumed to be 7% and muscle 43% of the body weight. One whole kidney was counted with a probe detector and compared with a renal standard of the same size and shape.

Blood clearance and urinary excretion were measured in n mal male volunteers following the intravenous administration of 0.5–1 mCi of ^{99m}Tc-GHA and ^{99m}Tc-DMS. The same data were obtained for ^{99m}Tc-iron-ascorbate in patients given 10–15 mCi for renal imaging whose subsequent radiographic and laboratory studies showed no evidence of renal disease or impairment of renal function. Multiple heparinized blood samples were taken at intervals from 5 min to 24 hr after injection, pipetted, and counted in a well detector in comparison with a standard. The percent administered dose in the circulating blood was calculated by assuming that the blood volume was 7% of the body weight. After blood centrifugation, aliquots of plasma were pipetted and counted. The percent dose in the plasma was calculated by assuming the plasma volume equaled the blood volume times the measured plasmacrit. The total plasma protein-bound activity was determined by counting before and after precipitation with trichloracetic acid, centrifugation, and removal of the supernatant.

The renal concentrations of GHA and DMS complexes of ^{99m}Tc were determined on two different occasions in six male volunteers at 1, 3, and 6 hr after injection. These measurements were performed with a 1½-in. crystal probe detector and flat-field collimator positioned posteriorly with the subject supine after the left kidney was carefully localized with a scintillation camera and external radioactive markers. The anterior precordial area (excluding the kidneys and liver) was counted and used to correct the renal counts for nonrenal activity. The net renal activity was compared with a 150-ml renal phantom of ^{99m}Tc in a Lucite scattering medium at the average depth of the kidneys. Corrections for variations in renal depth in different individuals did not improve the values obtained and were therefore omitted.

All distribution data given in the figures and tables were corrected for radioactive decay: the tabular data are mean values ± 1 s.d.

Selected ^{99m}Tc compounds were used for clinical studies. Fifteen millicuries of ^{99m}Tc-labeled iron ascorbate, mannitol, gluconate, glucoheptonate, lactobionate, or dimercaptosuccinate were administered intravenously to different patients and images of the kidneys were obtained up to 3 hr after administration. The relative perfusion of the kidneys was assessed by rapid serial images in the posterior projection, necessitating the large dose of ^{99m}Tc. In some patients images were obtained at 24 hr to examine the persistence of retention of the radioactivity in the renal cortex.

RESULTS

In the early phase of this study (*22,23*) evaluating the older agent technetium-iron-ascorbate complex, marked species differences in localization became apparent. At 1 hr after injection, the percent of the administered dose found in one kidney by organ assay in nonrodent species averaged 6.0% in man, 7.0% in the rhesus monkey, and 5.3% in the dog. However, different values were observed in rodent species—7.4% in the New Zealand rabbit, 10.3%

in the rat, and only 4.4% in the mouse. The blood clearance of this agent proved much slower in man. At 1 hr after injection, the blood level was approximately 17% in man whereas it was less than half this level in other species including the rhesus monkey. Similar marked species differences in concentration levels and rates of clearance have been observed for radiomercury-labeled chlormerodrin (*24*). For renal radiopharmaceuticals, therefore, it appeared that organ distribution data in rodents could be used only for comparison of one agent with another and not for radiation dose calculations valid for man.

Distribution in rodents. A survey of the organ distribution of 17 agents 1 hr after intravenous injection in rabbits is summarized in Table 1. Radiomercury-labeled chlormerodrin had the highest renal concentration and very favorable kidney-to-blood, kidney-to-liver, and kidney-to-muscle ratios. Its urinary excretion was relatively low. Two low molecular weight proteins, lysozyme and ribonuclease, were evaluated since many proteins with a molecular weight of less than 30,000 are known to concentrate and be metabolized in the kidney rather than in the liver and can be readily labeled with either radioiodine or ^{99m}Tc (*25*). Although their renal concentration proved greater than for the majority of agents tested, the blood and muscle concentrations were also relatively high.

DTPA, complexed with the long-lived nuclide ^{114m}In, was studied because cationic metallic chelates of this compound are considered to be "glomerular agents" undergoing passive diffusion through the glomerular membrane without tubular secretion or tubular resorption. Its renal concentration, cortex-to-medullary, and kidney-to-liver ratios are low.

Of many ^{99m}Tc agents, pertechnetate has the lowest renal concentration and its cortex-to-medullary ratio is less than one, indicating an absence of retention in the renal cortex. Its blood and liver concentrations at 1 hr are relatively high. Technetium-labeled human serum albumin was evaluated for comparison with other ^{99m}Tc complexes. As anticipated, its blood level at 1 hr remains very high. There is considerable concentration in the kidneys and urinary excretion, probably due to breakdown of the technetium-protein complex in vivo.

The distribution of many of the newer ^{99m}Tc renal radiopharmaceuticals is not significantly different from the older agent, technetium-iron-ascorbate complex. For example, the E. R. Squibb preparation (Renotec) (so-called ^{99m}Tc-DTPA) behaves biologically like technetium-iron-ascorbate except for a somewhat lower concentration in skeletal muscle. Its retention in the renal cortex is much higher than that obtained with a true technetium chelate of DTPA as previously reported in Atkins, et al (*26*). In this commercial preparation, therefore, the DTPA appears to act merely as a solubilizing agent for iron retarding the formation of hydroxides. The distribution of ^{99m}Tc-Sn-DTPA is similar but not identical to that of indium-chelated DTPA. The kidney-to-liver concentration ratio with either agent is unfavorable; the renal concentration of the ^{99m}Tc complex is slightly higher than the indium complex but low compared with other technetium agents used for renal imaging.

The agent, calcein blue labeled with ^{99m}Tc, was evaluated because it forms very stable chelates with calcium and other cations. It is rapidly excreted into the urine and has an extremely low renal concentration at 1 hr. Its high liver concentration is undesirable for renal studies. Technetium-labeled inulin, previously used for gamma cisternography, had a distribution completely different from that of the glomerular agent, ^{14}C-inulin, since the former undergoes considerable concentration in the renal cortex.

The ^{99m}Tc-labeled saccharides—mannitol, gluconate, glucoheptonate, and lactobionate—show no striking differences in organ distribution although their molecular weights vary. Their localization is like that of the technetium-iron-ascorbate complex except for lower concentrations in liver and skeletal muscle.

Dimercaptosuccinate has a very high concentration in the kidneys at 1 hr and an exceptionally high cortex-to-medullary ratio. Its blood clearance and urinary excretion are relatively slow. Despite the high absolute renal concentration at 1 hr, the kidney-to-blood, kidney-to-liver, and kidney-to-muscle concentration ratios are not greatly different from those of other agents. Technetium-labeled caseidin attains the highest renal concentration of any ^{99m}Tc-labeled radiopharmaceutical but its concentration ratios are not remarkable. The biologic localization of this polypeptide tends to resemble that of labeled low molecular weight proteins. These agents have not been widely used in man because they are foreign protein products and therefore potentially antigenic.

Changes in organ concentration of ^{99m}Tc-GHA and DMS in the rabbit at five different time intervals up to 24 hr are shown in Fig. 2. For GHA the maximal renal concentration occurred around 15 min and decreased approximately 50% by 24 hr. The concentration levels in other tissues also fell significantly by 24 hr. For DMS, the highest renal concentration occurred at 3 hr. By 24 hr, the concentration in the kidney and other organs fell only slightly. The renal cortex-to-medullary ratios for

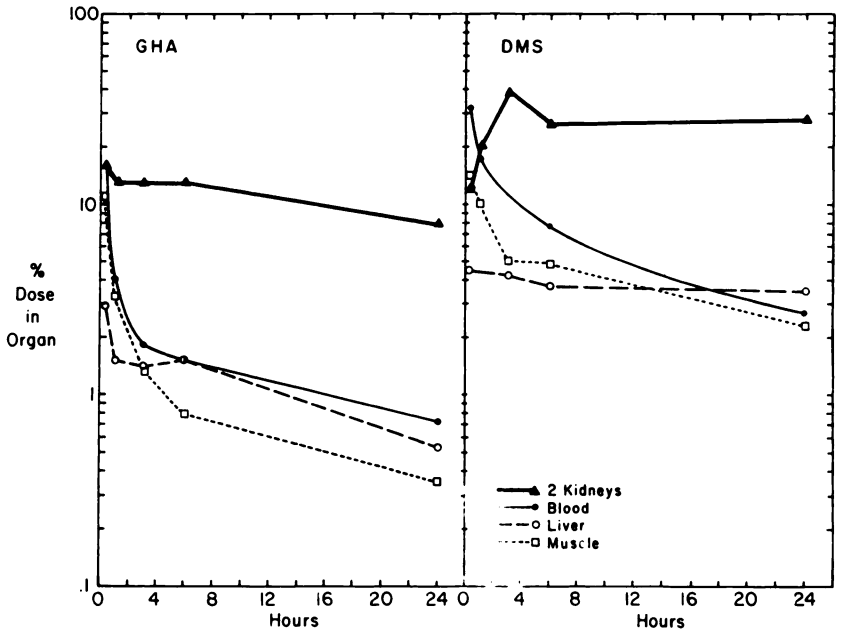


FIG. 2. Twenty-four-hour organ distribution of ^{99m}Tc-glucoheptonate (GHA) and dimercaptosuccinic acid (DMS) in rabbits, corrected for physical decay. Each point represents mean of six animals.

DMS were extremely high, particularly at 3 hr and beyond.

Distribution in dogs. In Table 2 the organ distribution of two newer agents, ^{99m}Tc-DMS and ^{99m}Tc-GHA, is compared with two older agents, ^{99m}Tc-iron-ascorbate and ^{203}Hg-chlormerodrin 1 hr after intravenous injection in dogs. For technetium-iron-ascorbate approximately 10% of the administered radioactivity is accounted for in the two kidneys, 3% in the liver, 3% in the gastrointestinal tract (of which half is in the small bowel), and 10% in skeletal muscle. Most of the gut activity is in the intestinal contents since about 4.5% of the administered activity is recovered in the feces at 24 hr. [illegible]gan distribution of ^{99m}Tc-GHA at 1 hr is like [illegible]hat of ^{99m}Tc-iron-ascorbate complex. The renal concentration of DMS at 1 hr is considerably higher than the other two technetium complexes and its kidney-to-liver concentration ratio is more favorable. None of these four agents has as high a renal concentration in the dog as in the rabbit.

Six dogs in the present series were given an intravenous injection of ^{131}I-serum albumin 15 min before sacrifice to define the intravascular volume of the major organs. In the liver and renal cortex the vascular volume represented 30% and 25%, respec-

TABLE 2. ONE-HOUR DISTRIBUTION OF AGENTS IN MONGREL DOGS

	^{99m}Tc-glucoheptonate	^{99m}Tc-iron-ascorbate	^{99m}Tc-2,3-dimer-captosuccinate	^{203}Hg-chlormerodrin
Percent dose in whole organ				
Normal kidney (one)	4.80 ± 6.70	5.30 ± 2.90	8.30 ± 5.20	13.00 ± 0.39
Percent dose/1% body weight				
Blood	0.44 ± 0.13	0.32 ± 0.14	0.77 ± 0.51	0.67 ± 0.39
Liver	0.74 ± 0.21	0.80 ± 0.63	0.77 ± 0.47	2.60 ± 0.92
Muscle	0.11 ± 0.03	0.09 ± 0.04	0.16 ± 0.09	0.34 ± 0.26
Small bowel and contents	0.25 ± 0.05	0.30 ± 0.21	0.41 ± 0.18	
Kidney	21.00 ± 8.20	22.00 ± 12.00	33.00 ± 20.00	48.00 ± 13.00
Cortex	19.00 ± 6.40	15.00 ± 6.20	33.00 ± 23.00	66.00 ± 15.10
Medulla	3.60 ± 2.40	3.00 ± 2.10	8.00 ± 8.40	7.40 ± 5.00
Ratios*				
Kidney/blood	50.00 ± 21.00	60.00 ± 28.00	58.00 ± 42.00	80.00 ± 40.00
Kidney/liver	31.00 ± 16.00	39.00 ± 36.00	53.00 ± 38.00	21.00 ± 8.20
Kidney/muscle	198.00 ± 57.00	188.00 ± 52.00	229.00 ± 120.00	260.00 ± 233.00
Cortex/medulla	5.10 ± 1.90	5.70 ± 3.10	7.10 ± 7.40	9.80 ± 5.80
No. of animals	13	8	16	12

* Ratios derived from 1% dose/1% body weight.

TABLE 3. BLOOD CLEARANCE OF ^{99m}Tc RENAL COMPLEXES IN HUMANS

	Percent dose technetium-iron-ascorbate complex (n = 12)			Percent dose technetium-glucoheptonate (n = 9)			Percent dose technetium-dimercaptosuccinic acid (n = 7)		
Time	Blood volume	Plasma volume	Plasma protein fraction	Blood volume	Plasma volume	Plasma protein fraction	Blood volume	Plasma volume	Plasma protein fraction
5 min	42.7 ± 12.0	34.6 ± 13.3	23.3 ± 9.2	32.9 ± 4.00	32.7 ± 3.90	15.4 ± 2.30	69.2 ± 6.90	69.2 ± 6.90	52.8 ± 3.30
15 min	28.9 ± 7.7	23.5 ± 10.3	14.9 ± 5.6	21.3 ± 3.50	21.1 ± 3.30	10.5 ± 2.50	55.6 + 5.80	55.6 ± 6.40	44.4 ± 9.40
30 min	21.9 ± 5.6	18.6 ± 6.0	11.1 ± 4.4	15.2 ± 2.70	15.1 ± 2.60	7.9 ± 1.70	43.0 ± 4.60	43.0 ± 5.10	33.3 ± 6.50
60 min	17.7 ± 5.3	13.1 ± 4.6	9.6 ± 3.3	11.4 ± 2.00	11.2 ± 2.10	6.1 ± 1.00	29.8 ± 3.90	29.8 ± 3.90	22.7 ± 4.70
90 min	—	—	—	9.2 ± 1.30	8.9 ± 1.10	5.2 ± 0.94	23.9 ± 2.30	23.8 ± 2.80	18.1 ± 3.90
3 hr	10.1 ± 3.5	8.6 ± 3.4	6.3 ± 2.2	6.6 ± 1.10	6.3 ± 1.20	4.5 ± 1.20	14.4 ± 1.20	13.8 ± 1.30	10.5 ± 1.60
6 hr	7.5 ± 2.9	6.1 ± 2.7	5.1 ± 2.8	5.1 ± 1.00	4.9 ± 1.00	3.8 ± 0.96	9.5 ± 1.00	9.4 ± 1.30	7.2 ± 1.30
24 hr	4.2 ± 1.9	4.0 ± 1.8	3.9 ± 1.1	3.1 ± 0.55	3.1 ± 0.57	2.7 ± 0.41	4.4 ± 0.54	4.3 ± 0.64	4.0 ± 0.65

tively, of the total organ volumes. In the small bowel only 5% and in skeletal muscle only 2.3% of the total organ volume was due to the vascular volume. From the organ and blood concentration levels of the radiopharmaceuticals in Table 2, the contribution of the residual intravascular activity to the total organ activity at 1 hr was calculated. For the liver it was estimated that 30% of the total organ activity at 1 hr was due to intravascular activity for DMS, 18% for GHA, and 12% for technetium-iron-ascorbate complex. For the other organs including the renal cortex the intravascular activity represented only a minor fraction of the total tissue activity.

Distribution in humans. The disappearance of three complexes of ^{99m}Tc, iron-ascorbate, GHA, and DMS, from the major blood components during the first 24 hr is summarized in Table 3. Whole blood disappearance curves for these three agents are illustrated in Fig. 3, together with previously reported values for ^{197}Hg-chlormerodrin (*27*), ^{99m}Tc-pertechnetate (*28*) and DTPA (*6*), and ^{113m}In-DTPA (*29*). The blood clearance of DMS is relatively slow, similar to that of pertechnetate, for about 6 hr but even slower than pertechnetate beyond this time. GHA has a relatively rapid blood clearance, identical with that reported for gluconate (*17*) and similar to that of ^{113m}In-DTPA for the first 2 hr but slower thereafter. Iron-ascorbate complex clears fairly rapidly for the first 6 hr or so but then slows markedly; by 24 hr residual blood levels are actually higher than those of pertechnetate.

For both DMS and GHA virtually all of the blood activity is in the plasma fraction with little or no diffusion into the red cells. Like gluconate (*17*), about 50% of the plasma activity of the GHA complex is loosely bound to plasma proteins initially, increasing to about 75% after 6 hr. For DMS about 75% of the plasma activity is loosely bound to plasma proteins in the first 6 hr, increasing to about 90% at 24 hr. For ^{99m}Tc-iron-ascorbate complex, about 80% of the total blood content is in the plasma fraction and the remaining 20% reversibly diffuses into the red cell volume. From 50 to 70% of the plasma activity is loosely bound to plasma proteins. Winston, et al (*30*) reported previously that 10% of the technetium-iron-ascorbate activity is protein-bound. For the DTPA chelate of ^{99m}Tc, only 5–10% of the serum activity is associated with serum proteins at 1 hr (*6*), and there is no diffusion into red cells (*31*).

Considering the plasma fraction alone, the plasma disappearance of DMS is slower than for the other

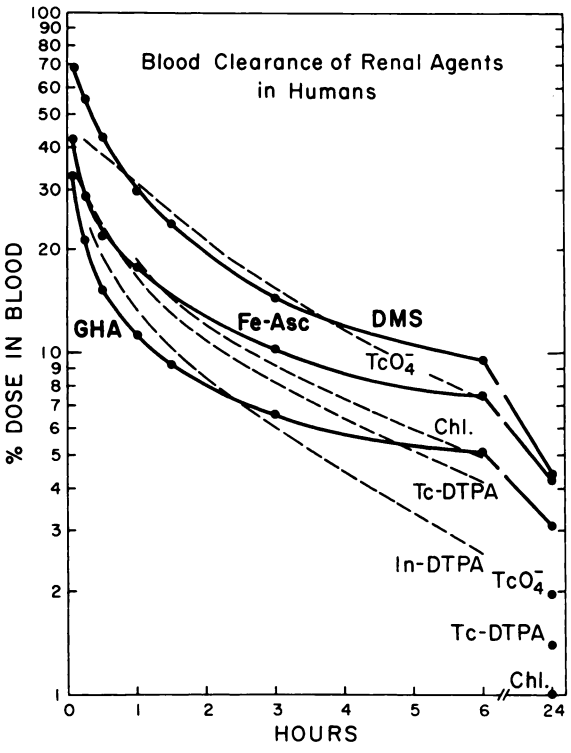


FIG. 3. Mean human blood clearance curves of renal agents during first 24 hr: ^{99m}Tc-labeled dimercaptosuccinic acid (DMS)—7 normal volunteers; glucoheptonate (GHA)—9 normal volunteers; iron-ascorbate (Fe-Asc)—12 patients without renal disease. Comparative blood disappearance curves from published sources—pertechnetate (TcO_4^-) (28); ^{197}Hg-chlormerodrin (Chl.) (27); ^{99m}Tc-DTPA and ^{113m}In-DTPA (29).

TABLE 4. CONCENTRATION OF RENAL RADIOPHARMACEUTICALS IN ONE HUMAN KIDNEY (CORRECTED FOR DECAY)

Agent	5–15 min	1 hr	3 hr	4 hr	6 hr	24 hr	4–6 days
^{99m}Tc-DMS		12.3	18.5		20.3		
^{99m}Tc-GHA		4.6	5.9		6.2		
^{99m}Tc-gluconate (17)	8.5	6.0					
^{99m}Tc-iron-ascorbate (33)		6.0					
^{99m}Tc-iron-ascorbate (34)		5.25			8.0	10.0	
^{99m}Tc-iron-ascorbate (36)	5.0			5.9		6.8	
^{99m}Tc-Renotec (26)	3.1	4.3		5.1		5.7	
^{99m}Tc-DTPA (26)	5.1	3.7		2.5			
Mercury-chlormerodrin (24)			16–22			8.0	
Mercury-bichloride (35)							26–27

TABLE 5. URINARY EXCRETION OF ^{99m}Tc COMPLEXES IN HUMANS

	^{99m}Tc-iron-ascorbate (n = 10)		^{99m}Tc-glucoheptonate (n = 9)		^{99m}Tc-2,3-dimercapto-succinate (n = 7)	
Time (hr)	Percent dose in urine	Cumulative percent urine	Percent dose in urine	Cumulative percent urine	Percent dose in urine	Cumulative percent urine
0–1	32.0 ± 4.7	32.0 ± 4.7	38.0 ± 6.50	38.0 ± 6.5	11.1 ± 3.70	11.1 ± 3.7
1–2			11.0 ± 2.10	49.0 ± 8.0	5.0 ± 0.96	16.1 ± 3.6
2–3			6.3 ± 0.65	55.3 ± 8.2	3.3 ± 1.40	19.4 ± 4.1
3–6			8.3 ± 1.90	63.6 ± 9.5	6.4 ± 1.00	25.8 ± 3.9
1–6	28.8 ± 5.7	60.8 ± 9.2	25.6 ± 2.90		14.7 ± 2.00	
6–24	12.8 ± 6.4	73.6 ± 10.2	7.5 ± 2.50	71.1 ± 11.0	11.0 ± 2.30	36.8 ± 4.2

complexes of ^{99m}Tc, thereby resembling ^{203}Hg-chlormerodrin. The plasma clearance of the GHA complex is relatively rapid. However, none of these agents clears as rapidly as ^{131}I-Hippuran. The iron-ascorbate complex clears rapidly for the first 2 or 3 hr, thereafter slowing. The plasma clearance of the DTPA chelate of ^{99m}Tc, previously studied by Hauser, et al (*6*), is slightly slower than ^{113m}In-DTPA or ^{51}Cr-EDTA chelates and considerably slower than ^{14}C-DTPA (*32*).

The mean concentration of ^{99m}Tc complexes of DMS and GHA in the left kidney in six normal volunteers, as determined by probe counting, is listed in Table 4, together with comparative data of other agents reported previously (*17,24,26,33–36*). The renal concentration of ^{99m}Tc-GHA in the human is similar to the direct assay values in the dog and not significantly different from the published values for the iron-ascorbate or gluconate complex. The renal accumulation of ^{99m}Tc-DMS is definitely greater than for other technetium complexes and increases at least up to 6 hr following injection. The renal concentration levels in humans are higher than those obtained in the dog. DMS is the only ^{99m}Tc agent to date reaching the high renal concentration of radiomercury-labeled chlormerodrin (*24*).

The urinary excretion of ^{99m}Tc complexes of GHA and DMS in humans is summarized in Table 5. The cumulative urinary clearance of these complexes is compared with that of other agents evaluated previously (*6,24,37*) during the first 24 hr in Fig. 4. The urinary clearance of DMS is very slow but faster than pertechnetate. Initially, the urinary excretion of the GHA complex is faster than that of the iron-ascorbate complex but the cumulative excretion by 24 hr is equal. About 30% of an administered dose of ^{99m}Tc-iron-ascorbate is excreted as pertechnetate (*33*). The 1-hr excretion of ^{99m}Tc-gluconate measured in only one patient (*17*) was 36%, apparently similar to that of GHA. The urinary excretion of the DTPA chelate of ^{99m}Tc is higher than that of the other technetium complexes.

Clinical evaluation. Selected representative renal images are shown in Fig. 5 obtained with a scintillation camera following the intravenous injection of 15 mCi of the various ^{99m}Tc agents in patients without evidence of renal disease. Pertechnetate was of value only for "first transit" rapid serial images following an intravenous bolus injection to compare the relative perfusion of the two kidneys. Even at 1 min after injection and thereafter, the kidneys were not well demonstrated with this material because of the high concentration in the surrounding organs.

With ^{99m}Tc-Sn-DTPA the most satisfactory images were obtained 10–15 min after injection. Activity was usually visible in the pelvocalyceal collecting

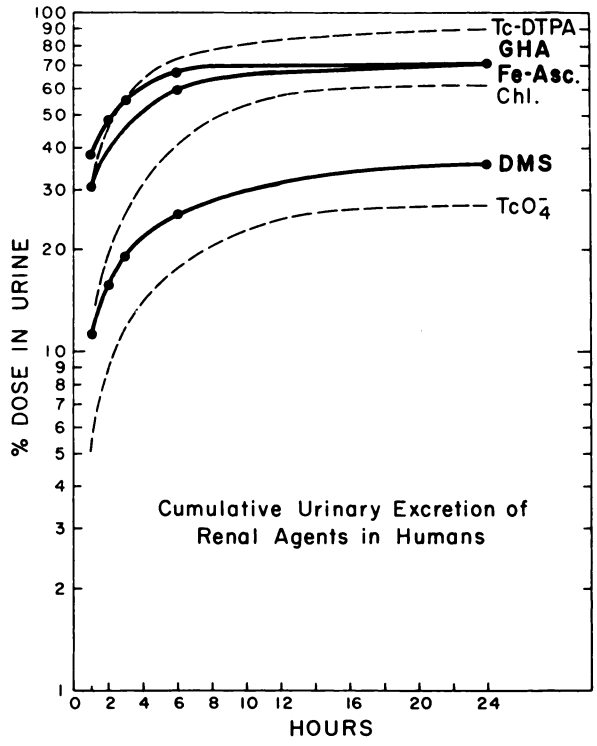


FIG. 4. Mean cumulative urinary excretion curves up to 24 hr: ^{99m}Tc-labeled DMS—7 normal volunteers; GHA—9 normal volunteers; iron-ascorbate (Fe-Asc)—18 patients. Comparative curves of other agents are from published sources (6, 24, 37).

system in addition to the renal parenchyma. By 1 hr, however, the parenchymal images faded. Consequently, it proved difficult to obtain high-resolution images of the cortex without pelvocalyceal activity. Like ^{131}I-Hippuran, it demonstrated obstructive uropathy or localized abnormalities of the renal collecting system but sometimes failed to demonstrate small focal lesions of the parenchyma because of its lack of cortical retention.

Technetium-99m-labeled iron-ascorbate, gluconate, glucoheptonate, lactobionate, and mannitol produced similar renal images clinically. Serial images from 1 to 5 min demonstrated the renal parenchyma well without any activity in the renal calyces or pelvis. The latter structures were often seen by 10 or 15 min and occasionally up to 1 hr. Details of the renal parenchyma were best demonstrated 1 hr or later because of the clearance of activity from the surrounding organs and retention of these agents in the renal cortex. The gallbladder was seen occasionally, particularly in anterior views, with any of these agents.

Images following the intravenous injection of ^{99m}Tc-DMS complex showed a progressive accumulation in the renal parenchyma at least up to 6 hr, usually without any visible radioactivity in the renal collecting system. In early images from 1 to 5 min, there is often faint visualization of the bone marrow in the lumbar spine that disappears later. At this early time interval, the kidneys are not visualized as well as with GHA because of the relatively high surrounding activity. Occasionally there is faint visualization of the abdominal aorta for several minutes due to the high blood level. On delayed images, 1 hr

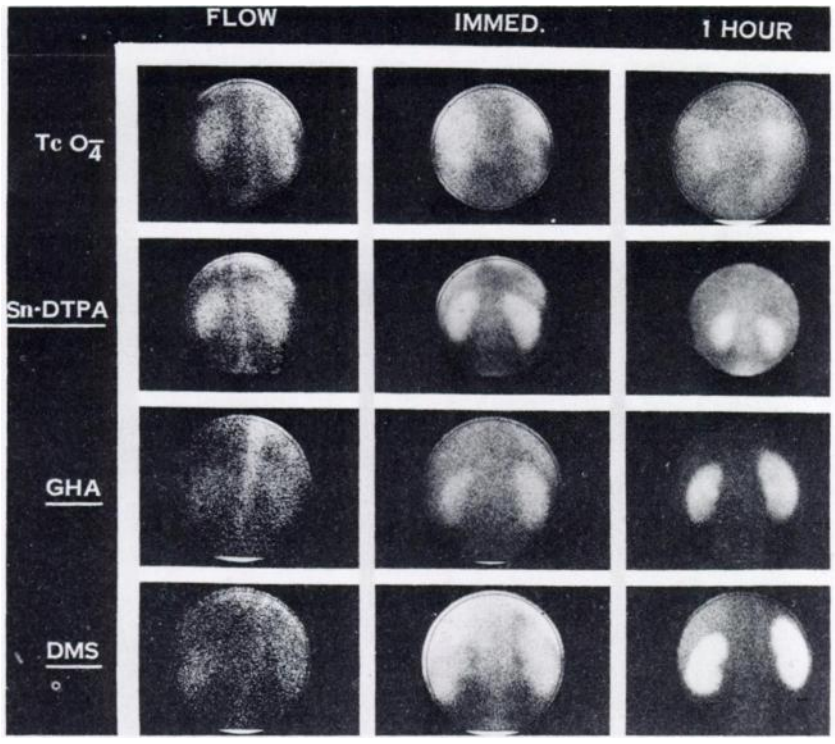


FIG. 5. Renal images obtained with 15 mCi of various ^{99m}Tc agents in patients without evidence of renal disease. Renal collecting system is well demonstrated early with GHA and DTPA complexes. Renal parenchyma above is well demonstrated in delayed images with DMS and in "immediate" images (from 1 to 5 min) and delayed images with GHA.

TABLE 6. RADIATION DOSE ESTIMATES FOR RENAL ^{99m}Tc COMPLEXES (RADS/mCi)

	DMS	GHA	Iron-ascorbate (Ref. 6)	DTPA (Ref. 6)	Gluconate (Ref. 7)
Renal cortices	0.76	0.20			
Whole kidneys	0.62	0.17	0.27	0.042	0.21
Bladder mucosa	0.28	0.80		0.55	0.12
Liver	?0.02	?0.01			
Ovaries	0.022	0.020		0.019	
Blood	0.019	0.010			
Total body	0.016	0.007	0.008	0.016	0.006

or later, parenchymal defects corresponding to the medullary pyramids are often seen normally and are due to the high differential in uptake between the cortical and medullary tissue. Some activity is invariably seen in the liver when this organ is included in the field of view as with all other ^{99m}Tc complexes in the current study.

Radiation dose estimates. Based on the present distribution data obtained in humans, radiation dose estimates were calculated for ^{99m}Tc-labeled DMS and GHA (summarized in Table 6) using the methods of the MIRD Committee (*38,39*). For the absorbed radiation dose for the bladder wall and ovaries, "S" factors (*40*) (absorbed dose per unit cumulated activity) were used. For DMS, 44% of the administered dose localized in the two kidneys, with a biologic uptake half-time of 1 hr and without biologic excretion (resultant effective half-time 5.1 hr). The mean blood disappearance curve was resolved into three exponential components—12% with a biologic half-time of 18 hr, 44%, 50 min, and 44%, 20 min (resultant effective half-time, 54 min). The total-body retention had a biologic half-time of 72 hr for 80% of the dose and 1.6 hr for 20% (resultant effective half-time 5.4 hr). For GHA, 14.6% of the dose localized in the two kidneys with a biologic uptake half-time of 45 min and a biologic half-time of excretion of 24 hr (total effective half-time 4.1 hr). Its blood clearance had three exponential components, with biologic half-times of 24 hr (6%), 1 hr (10%), and 5 min (84%) (resultant effective half-time 27 min). The total-body retention of GHA had three components, 35% with a biologic half-time of 89 hr, 30% with a half-time of 2.4 hr and 35% with a half-time of 20 min (resultant effective half-time 2.6 hr). The total-body retention of both agents was based on the mean cumulative urinary excretion. The hepatic radiation dose estimates were less certain since they had to be based on distribution data in the dog rather than on human measurements. For the radiation dose to the bladder wall from its urinary content of radioactivity, it was assumed that the urine flow rate was 60 cc/hr, that there were three daytime voidings every 4 hr, and one overnight void, and that the injection of the radioactive dose was given when the bladder was empty.

Table 6 shows that for most organs the radiation dose from ^{99m}Tc-DMS is considerably higher than for the GHA complex because the renal concentration and effective half-time of the latter are considerably lower. It may therefore be justified to use larger administered doses of the GHA complex clinically. The only structure to receive a larger radiation dose from GHA than DMS is the bladder mucosa due to the rapid elimination of a large component of GHA via the urine. The dose estimates to the bladder mucosa in Table 6 are for the "worst situation." The bladder wall dose is significantly reduced under different physiologic conditions i.e., when the bladder is partially filled at the time of injection or when the rate of urine flow is increased by hydration. The bladder dose is decreased only slightly by more frequent daytime voidings. Based on the above radiation estimates, administered doses of 10–15 mCi of ^{99m}Tc-DMS and even somewhat larger doses of ^{99m}Tc-GHA appear reasonable.

DISCUSSION

In the selection of a complex of ^{99m}Tc for renal imaging, the following biologic characteristics should be considered:

1. It should reach a high absolute concentration in the kidneys (expressed as a percentage of the administered radioactivity) within 1 or 2 hr after intravenous injection.
2. Its concentration in organs and tissues adjacent to the kidney, particularly the liver, should be low.
3. Its clearance from blood and extravascular fluid compartments should be rapid since the skeletal muscle and connective tissues overlying the kidneys tend to reflect the extracellular fluid concentration.
4. Its concentration in the gastrointestinal tract should be low. Radioactivity in the gastrointestinal contents may be due to biliary excretion of the agent or to excretion by the intestinal mucosa itself.
5. Like other radiopharmaceuticals it should be free from pharmacologic and toxic effects and the radioactive complex should be stable in vivo and in vitro.

Any water-soluble ^{99m}Tc agent including pertechnetate injected as a bolus intravenously is satisfactory for rapid serial "first transit" images to show the

relative perfusion of the two kidneys. Because pertechnetate is neither cleared rapidly by the kidneys nor concentrated in the renal cortex (*24*), it is unsatisfactory for renal imaging after the initial vascular transit.

Technetium-99m-Sn-DTPA is cleared more rapidly than pertechnetate by glomerular filtration without tubular resorption. Hence, it promptly appears in the urine and the pelvocalyceal system is well visualized by imaging. Only a small fraction of the agent is retained in the cortex (*25*). Consequently, visualization of small parenchymal defects is not always achieved.

Several labeled saccharides including ^{99m}Tc-GHA and ^{99m}Tc-gluconate exhibit a biologic behavior similar to ^{99m}Tc-iron-ascorbate complex. A sizable fraction of the injected radioactivity is promptly excreted into the urine. The resultant visualization of the pelvocalyceal collecting system is helpful in the diagnosis of such conditions as obstructive uropathy and chronic pyelonephritis. About 6% of the administered dose of these agents, however, is retained by each kidney, largely in the cortex. Previous autoradiographic studies in rats (*41*) showed that this residual ^{99m}Tc-iron-ascorbate is localized intracellularly, probably in the proximal convoluted tubules. Because of the cortical retention, visualization of the parenchyma on delayed images is excellent as the activity in the surrounding tissues falls.

These labeled saccharides overcome some of the practical shortcomings of the iron-ascorbate complex. Change in this complex occurs on standing even after short intervals of 1 hr as demonstrated by paper chromatography (*29*). It is likely that a fine particle colloid of ferric hydroxide eventually forms. Hauser, et al (*6*) believe that this product contains two components—a complex of ascorbate that passes through a sephadex column and a hydrolysis product of ^{99m}Tc that does not. Moreover, this agent has been difficult to formulate in an "instant sterile kit." On the contrary, ^{99m}Tc-gluconate and GHA are readily prepared as a "sterile kit" and produce reliable, consistent clinical results. We have found them very satisfactory for routine renal imaging for visualizing abnormalities of both the pelvocalyceal collecting system and the renal parenchyma.

Technetium-DMS was designed as a renal agent to replace mercury-labeled chlormerodrin (*19*). The high absolute renal concentration of DMS is about twice that of other ^{99m}Tc complexes in man, approaching that of labeled chlormerodrin. The plasma clearance of DMS is similar to that of chlormerodrin (*42*) but its blood clearance is slower. The urinary excretion of DMS is extremely slow so that the pelvocalyceal system is visualized poorly or not at all. It is an excellent agent for delayed imaging of the parenchyma after 1–6 hr or beyond for the detection of small focal lesions such as masses, infarcts, or pyelonephritic scars. Because this agent oxidizes spontaneously, it must be used soon after the ^{99m}Tc eluate is added to the sterile kit.

The present work shows that tissue radioassay of experimental animals, particularly rodents, cannot be used to quantitate the biologic distribution and fate of renal radiopharmaceuticals in man. Such experiments, however, are helpful for the qualitative comparison of one agent to another in the same species.

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