RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Binding of Technetium-99m to Plasma Proteins: Influence on the Distribution of Tc-99m Phosphate Agents

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Plasma protein binding of Tc-99m was assessed in man after injection of various Tc-99m-labeled bone imaging agents. Of the five methods in which plasma proteins were precipitated to determine protein binding no correlation between them could be established. The ammonium sulfate method seemed to correlate well with dialysis filtration. Plasma obtained from patients injected with Tc-99m phosphate compounds was reinjected to rats. The bone uptake in these animals correlated linearly with the unbound activity in the injected plasma. Provided that no protein binding would occur, the bone uptake as well as the urinary excretion proved to be identical for Tc-99m HEDP, MDP, and PPi. Electrophoresis of Tc-99m PPi indicated that the intact complex may be uncharged, whereas at low ligand concentrations uncharged as well as negatively charged Tc-99m species are formed. Better methods are needed, however, to establish the presence of various Tc-99m species and their relative role in the kinetics of these compounds, and plasma protein binding.

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Several chelating phosphate compounds, labeled with reduced technetium-99m, have been proposed for bone imaging (*1–8*). Today only Tc-99m ethane-1, hydroxy-1, 1-diphosphonate (HEDP), -methylenediphosphone (MDP), and -pyrophosphate (PPi) are in clinical use. Although the in vivo distribution patterns of these bone imaging agents are similar, a number of studies revealed significant differences in the biokinetics of the Tc-99m phosphate agents (*9–12*). Differences in plasma protein binding of technetium might be responsible for this. This study was undertaken to determine these differences.

MATERIALS AND METHODS

The following phosphate compounds were used in this study.

Lyophilized kits. HEDP I: 5 mg ethane-1, hydroxy-1, 1-diphosphonate* 0.25 mg $SnCl_2 \cdot 2H_2O$. MDP: 5 mg methylenediphosphonate* 0.40 mg $SnCl_2 \cdot 2H_2O$. PPi I: 20 mg hydrated pyrophosphate† 4 mg $SnCl_2 \cdot 2H_2O$.

In house preparations. Tripolyphosphate: 20 mg hydrated tripolyphosphate (TriP), 1 mg $SnCl_2 \cdot 2H_2O$, dissolved in 0.4 ml water. PPi II: 40 mg hydrated pyrophosphate, 4 mg $SnCl_2 \cdot 2H_2O$ in 0.5 ml water. HEDP II: 20 mg ethane-1, hydroxy-1, 1-diphosphonate, 1 mg $SnCl_2 \cdot H_2O$, contents of four kits HEDP I. Tripolyphosphate‡ was purified by recrystallization from 25% methanol in water (*13*).

A mixture of pyrophosphate or tripolyphosphate and tin(II) chloride was dissolved in water and the pH was adjusted to pH 6.8 with 0.2 *N* HCl. The final solution was pressed through a 0.22 μm Millipore filter and 0.4–0.5 ml were filled in evacuated vials and kept deep frozen until use.

Fifteen mCi of [^{99m}Tc]pertechnetate in isotonic saline, obtained from a fission molybdenum generator were added to each kit or preparation. The final volume of all preparations was 4 ml.

All radiopharmaceuticals, including [^{131}I]ortho-

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iodohippurate, were administered intravenously to patients with normal bone scans. Blood was collected by venipuncture at various times after injection, heparinized, and the plasma separated by centrifugation.

Special Tc-99m PPi preparations. The final volume of all these preparations was 100 ml. All reagent solutions were kept free of air and carbon dioxide through purging with purified nitrogen. A $0.5 \cdot 10^{-3}$ *M* solution of pyrophosphate and a $0.1 \cdot 10^{-3}$ *M* solution of tin(II) chloride was freshly prepared in 10 ml water, and 1 ml each of these solutions was added to the reaction vessel, containing isotonic saline. The pH was adjusted to 7.0 with hydrochloric acid. Finally 30–300 mCi [^{99m}Tc] pertechnetate was added and 30 min of equilibration was maintained. This Tc-99m pyrophosphate preparation was diluted in neutral isotonic saline and also in phosphate buffered saline with a pH of 7.3, containing 7.66 g NaCl, 0.202 g KH_2PO_4, and 0.923 g $NA_2HPO_4 \cdot 2H_2O$/1 H_2O and 30 min equilibration was again maintained.

Determination of plasma protein binding. The protein binding of Tc-99m and I-131 in human plasma was determined at various times after administration of Tc-99m PPi, HEDP, pertechnetate, and [^{131}I]ortho-iodohippurate. The same five patients were used for one radiopharmaceutical and for all six methods for separation of the plasma proteins from plasma water.

Plasma, 1 ml, was mixed with 2 ml each of uranylacetate (1.6%), alcohol (96%), trichloroacetic, or perchloric acid (20% each) and the precipitated proteins were separated by centrifugation. Three milliliters plasma were added to 1.5 g ammonium sulphate. After complete dissolution the proteins were separated by pressing through a 0.22 μm Millipore filter. Also 4 ml plasma were filtered by means of dialysis.‖

Since it is possible that any Tc-99m colloid present in plasma might also have been removed by filtration, blank experiments were conducted in which untreated plasma was pressed through the filter. The activity in plasma, however, remained unchanged.

The Tc-99m activity in plasma was compared with that in the protein-free aqueous component. A correction was made for the volume diminution after the removal of the proteins and for the volume expansion after the dissolution of ammonium sulphate. By means of the Biuret reaction it was shown that more than 90% of the plasma proteins were separated from plasma water.

Animals experiments. The effect of protein binding of Tc-99m in human plasma on the biodistribution of Tc-99m phosphate agents was studied by injecting into rats the same human plasma in which protein binding has been determined.

Immature male Wistar rats (170–190 g) were used in these studies. Narcosis was achieved by intraperitoneal injection of pentobarbital. Plasma collected from each of seven patients at various times after injection of 15 mCi of the Tc-99m-labeled phosphate compounds, were injected into the tail vein of two rats. In addition to the

TABLE 1. COMPARISON OF VARIOUS METHODS FOR DETERMINATION OF THE PLASMA PROTEIN BINDING IN MAN OF Tc-99m-PPI, HEDP, PERTECHNETATE AND [^{131}I] ORTHO-IODOHIPPURATE AT VARIOUS TIMES AFTER INJECTION (N = 5)*

	Ammonium sulphate	Uranylacetate	Alcohol	Trichloroacetic	Perchoric Acid	Filtration
10 min†	19.5 ± 4.57	98.8 ± 0.35	96.7 ± 1.37	93.3 ± 2.57	50.0 ± 8.34	51.5 ± 2.90
1 hr	34.2 ± 5.31	97.0 ± 0.87	91.9 ± 2.62	90.3 ± 3.71	61.9 ± 9.87	60.2 ± 1.72
2 hr	54.5 ± 6.52	96.0 ± 1.46	90.4 ± 3.20	86.4 ± 4.80	62.2 ± 5.81	69.4 ± 6.55
3 hr	66.7 ± 7.91	96.0 ± 1.21	90.0 ± 4.17	86.2 ± 4.34	72.3 ± 5.00	76.8 ± 5.86
10 min‡	9.76 ± 4.42	99.3 ± 0.14	98.1 ± 0.39	84.3 ± 5.26	27.1 ± 6.73	41.4 ± 5.43
1 hr	12.9 ± 3.88	98.4 ± 0.93	96.8 ± 0.29	83.3 ± 4.42	28.7 ± 5.56	43.3 ± 4.28
2 hr	14.5 ± 2.55	97.9 ± 1.77	95.5 ± 1.01	77.6 ± 7.89	28.3 ± 1.45	44.1 ± 4.11
3 hr	18.0 ± 2.19	97.6 ± 1.47	95.0 ± 1.71	72.0 ± 7.79	24.6 ± 2.93	46.3 ± 4.32
10 min‖	82.9 ± 2.93	74.3 ± 1.88	8.32 ± 4.82	35.9 ± 2.28	8.70 ± 1.86	82.6 ± 2.52
1 hr	81.9 ± 2.92	73.7 ± 4.72	6.80 ± 7.15	33.5 ± 4.04	9.58 ± 3.54	81.5 ± 3.22
10 min§	98.6 ± 0.29	83.3 ± 1.33	8.76 ± 4.67	25.6 ± 2.26	18.9 ± 1.58	73.4 ± 2.83
1 hr	98.0 ± 0.41	85.1 ± 0.79	10.3 ± 2.80	30.4 ± 4.50	25.8 ± 1.89	74.3 ± 2.71

* Values shown are percent protein bound fraction of activity present in plasma at times shown. This is not based on total injected dose.

† Tc-99m PPI (40 mg PPi).

‡ Tc-99m HEDP (20 mg EHDP).

‖ [^{99m}Tc] pertechnetate.

§ [^{131}] ortho-iodohippurate.

1 ml of plasma to each rat, 1 ml of isotonic saline was also injected to produce a uniform diuresis.

One hour after injection, the animals were decapitated and the activity in blood, urine, the right femur, and other organs was determined. The penis was ligated before injection and the whole bladder was removed afterwards. Six percent of body weight was assumed to be blood and bone (normally 10% bone). The latter correction was necessary because of an increased uptake in the growth plate of the femur in young rats (*19*).

Electrophoresis. The charge of technetium in the special Tc-99m PPi preparations was determined by means of electrophoresis. A glass tube with a diameter of 1 cm was used. The platinum electrodes were fixed in an upright position 32 cm apart, two auxiliary electrodes were positioned at a distance of 24 cm. A constant voltage of 150 V was maintained between the latter electrodes, using a voltage meter with an internal resistance of 1.10^{12} ohm. To avoid heat circulation, the glass tube was filled with purified sea sand. No other carrier was used to minimize absorptive effects. The same oxygen-free solutions in which the Tc-99m preparations had been made were used as a solvent. A constant temperature of 35°C was thermostatically maintained in a water bath. The whole device was placed on a large field gamma camera and the migration of Tc-99m was observed by cinescintigraphy. Immediately before the electrophoresis was started, about 10 μl of the Tc-99m preparation were placed in the middle of the glass tube by means of a syringe and a long aspirating needle.

RESULTS

Comparison of various methods for determination of protein binding. The results of plasma protein binding determined by different methods are shown in Table 1. The values for each of the radiopharmaceuticals are neither unequivocal nor comparable, for different methods for determination of protein binding. This is not only true for the Tc-99m phosphate agents but also for the well defined compounds like $^{99m}TcO_4^-$ and [^{131}I]-ortho-iodohippurate. When the ammonium sulphate method was used, the protein binding of Tc-99m seems to increase strongly after administration of both Tc-99m phosphate agents. To a lesser degree this finding was confirmed by the dialysis filtration method.

The reliability of the dialysis filtration method was checked by filtrating one plasma sample over a longer period and by collecting the plasma water in various fractions. The Tc-99m activity in the plasma water increased constantly by a factor of ten within 60 min of filtration, indicating that the filter membrane became more and more permeable to Tc-99m and that the measured protein binding of Tc-99m will depend on the duration of filtration.

Protein binding of Tc-99m in human plasma. The plasma protein binding of Tc-99m in man after administration of four different Tc-99m phosphate agents (Tc-99m HEDP I, MDP, PPi I, and TriP(tripolyphosphate) is compared in Table 2. The protein binding of Tc-99m was assessed by the ammonium sulphate method and was followed for up to 4 hr after injection. In all cases the protein binding fraction of the total activity in the plasma increased with time after injection but differed significantly from each other depending on the phosphate compound administered. The lowest plasma protein binding fraction of Tc-99m was found in the case of Tc-99m HEDP, followed by Tc-99m MDP, PPi, and TriP. The protein binding fraction of Tc-99m in the case of Tc-99m HEDP and PPi was comparable to that of the preparations used in the first part of this study (Table 1), which contained more of the chelating phosphate compounds.

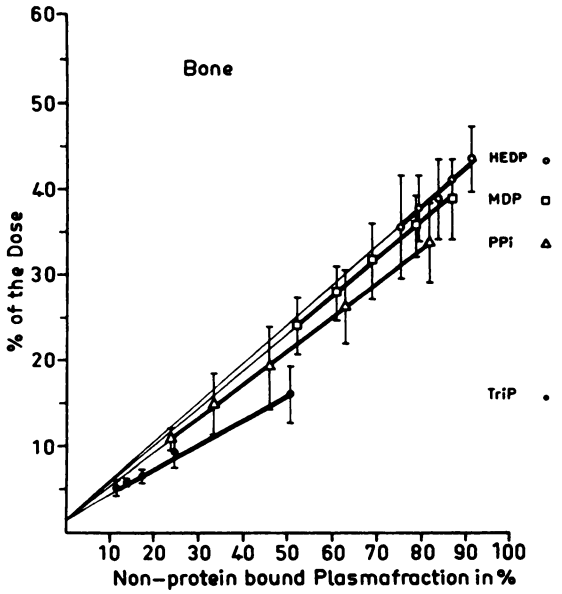
TABLE 2. PLASMA PROTEIN BINDING OF Tc-99m AFTER ADMINISTRATION OF Tc-99m PHOSPHATE AGENTS (N = 5)*

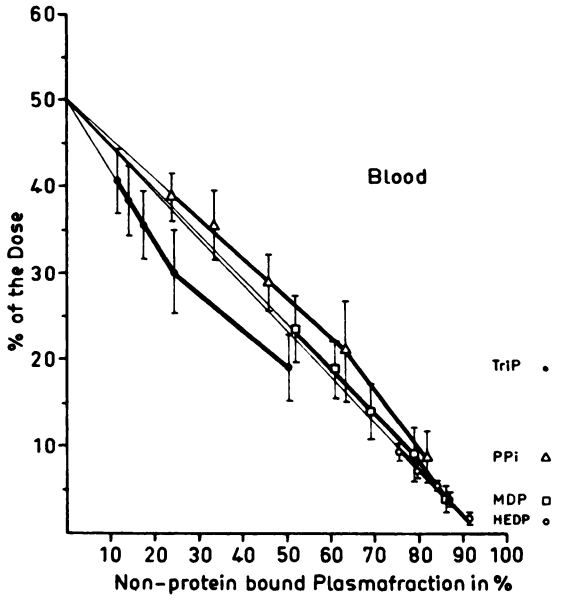
	10 min	1 hr	2 hr	3 hr	4 hr
Tc-99m HEDP (5 mg HEDP)	8.65 ± 2.55	12.8 ± 2.49	16.0 ± 2.81	20.5 ± 4.53	24.5 ± 3.73
Tc-99m MDP (5 mg MDP)	13.3 ± 4.29	22.4 ± 3.80	31.4 ± 4.96	39.6 ± 5.23	48.0 ± 4.72
Tc-99m PPi (20 mg PPi)	18.2 ± 4.12	36.8 ± 3.13	54.0 ± 4.66	66.5 ± 4.15	79.3 ± 4.02
Tc-99m TriP (20 mg TriP)	49.6 ± 8.78	75.1 ± 2.62	82.5 ± 3.82	86.1 ± 3.57	90.0 ± 3.66

* Values shown are percent protein bound of total activity present in plasma at various times after injection in 15 normal patients (ammonium sulfate method).

Animal experiments. The 1 hr organ distribution of Tc-99m in the rat was correlated with the nonprotein bound plasma fraction of Tc-99m in human plasma. With respect to bone uptake, a good correlation between both parameters was found for all Tc-99m phosphate agents (Fig. 1). Technetium-99m phosphate agents with a lower binding of Tc-99m to human plasma proteins were taken up in the bone to a greater extent than those agents with a strong protein binding of Tc-99m. A mathematical analysis of these results revealed a linear correlation between both parameters.

In general, similar results were obtained for the urinary excretion of Tc-99m in the rat with only one exception, Tc-99m TriP (Fig. 1). The urinary excretion of Tc-99m was much greater than that observed for the other agents with weaker Tc-99m protein binding. Consequently the Tc-99m blood activity related to protein binding of Tc-99m was the lowest detected in the case of Tc-99m TriP. If all Tc-99m in human plasma





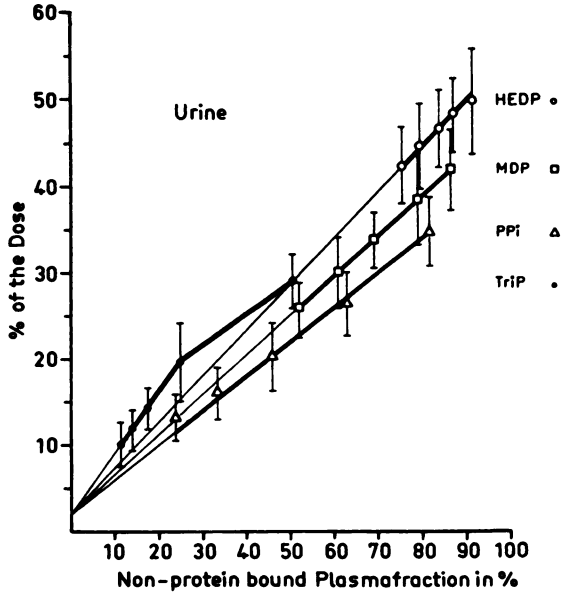


FIG. 1. Correlation between nonprotein bound Tc-99m in human plasma and 1 hr distribution of Tc-99m in rat (N = 14 for each point). Plasma samples collected at various times (10 min to 4 hr) after injection of Tc-99m phosphate agents in man. Protein binding of Tc-99m in human plasma was assessed by means of ammonium sulphate and same plasma was injected into two rats simultaneously.

were bound to proteins, about 50% of the injected Tc-99m activity would be found in the whole blood of the rat 1 hr after injection (Fig. 1).

The Tc-99m uptake in the other organs investigated was low and in general similar to the blood concentrations and has therefore not been presented. No linear correlation between the nonprotein bound Tc-99m fraction and the Tc-99m concentration in the rat kidneys was found.

The Tc-99m bone uptake in the rat was also correlated with in vivo distribution time in man and the rat (Fig. 2). The distribution time in man varied from 10 min to 4 hr whereas a constant and additional distribution time of 1 hr was maintained in the rat. The decrease in Tc-99m bone uptake in the case of Tc-99m HEDP, MDP, and PPi could be most adequately represented as a simple exponential function ($\log y = a + bx$), in the case of Tc-99m TriP it was a hyperbolic function ($\log y = a + \log bx$). The Tc-99m bone uptake in the rat was uniformly 47% of the dose at a time $x = 0$, in the case Tc-99m TriP this could not be predicted.

Similar results were obtained for the urinary excretion and blood concentration of Tc-99m. None of the usual functions could express the kinetic data in the case of Tc-99m TriP. In the case of Tc-99m HEDP, MDP, and PPi the 1 hr urinary excretion of Tc-99m would be 50% of the dose at time $x = 0$.

Electrophoretic studies. The charge of the Tc-99m compounds formed at different PPi concentrations in the equilibrium was studied by means of electrophoresis (Fig. 3). All experiments were carried out three times, the migration distances of [^{99m}Tc]pertechnetate and [^{131}I]iodide (both one negative charge), of [^{51}Cr]chromate (two possible negative charges) and of [^{85}Sr]-chloride (two possible positive charges) were used as a standard. No exact correlation was found between the expected charge units and the migration distances of these ions. Since the migration rate in water will not only depend on the charge but also on the radius of the ion and since the radius of the Tc-99m compounds investigated was unknown, no definite charge units can be concluded by these experiments.

No movement at all of Tc-99m was observed when Tc-99m PPi was prepared in isotonic saline at a PPi concentration of $500 \cdot 10^{-6}$ *M*. At a PPi concentration of $10 \cdot 10^{-6}$ *M* two Tc-99m fractions were noticed. About

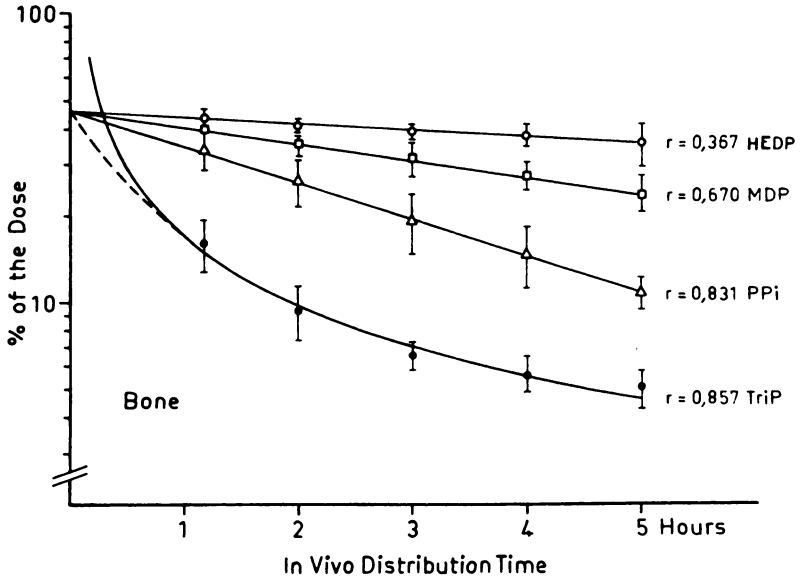


FIG. 2. Correlation between 1 hr bone uptake of Tc-99m in rat and time when plasma samples were obtained from man (additional 1 hr distribution in the rat, N = 14 for each point).

90% of the Tc-99m activity did not show any migration. The remaining 10% of activity carried the same negative charge as [^{99m}Tc]pertechnetate and is considered as this compound which has already been in the preparation. When Tc-99m PPi was prepared in a weakly buffered saline with pH 7.3 at a PPi concentration of $10 \cdot 10^{-6}$ *M* two Tc-99m fractions arose. About 70% of the activity was uncharged, the remaining activity was spread between zero and the −2 charge reference distance of [^{99m}Tc]pertechnetate, indicating that the charged Tc-99m fraction was formed continuously during the electrophoresis.

DISCUSSION

The protein binding of technetium from Tc-99m-labeled phosphate compounds is well documented in the literature (*11, 14, 15,* phosphate: *16–18*). However the methods used in these determinations may not be the best. The data shown in Table 1 clearly indicate that none of the reagents give any consistent correlation regarding protein binding. Of all the reagents tested, for the phosphate compound at least, the ammonium sulfate precipitation method seemed to compare well with the dialysis filtration.

Human plasma protein bound fraction data shown in Table 2 indicate an increase in the protein bound activity with time. It must be noted, however, that the fraction of injected dose remaining in the plasma decreases considerably with time reaching as low as 4–12% of the total injected dose at 3 hr. If the protein bound activity in the plasma is expressed in terms of total dose injected, the actual protein binding decreases with time (*14, 16*). This rate of decrease depends on the individual phosphate compound. HEDP seems to have the least protein binding and TriP has the most.

The electrophoresis method did not yield any conclusive result on charge units but electrophoresis of Tc-99m PPi indicated that the intact complex may be uncharged, whereas at low ligand concentrations uncharged as well as negatively charged Tc-99m species different from free TcO_4^- are formed. After an equal dilution of Tc-99m PPi before injection, Tc-99m was not further localized in bone and its biodistribution resembled that of reduced technetium (*18*). Protein binding of Tc-99m was increased when the dilution was made in a weakly buffered saline instead of normal saline (*17, 18*). It was suggested that protein binding of Tc-99m is due to a charged technetium(IV) species not further complexed with the phosphate compound (*18*).

The nonprotein bound Tc-99m fraction in the human plasma had a linear correlation with the bone uptake in rats (Fig. 1). This indicates that the protein binding is

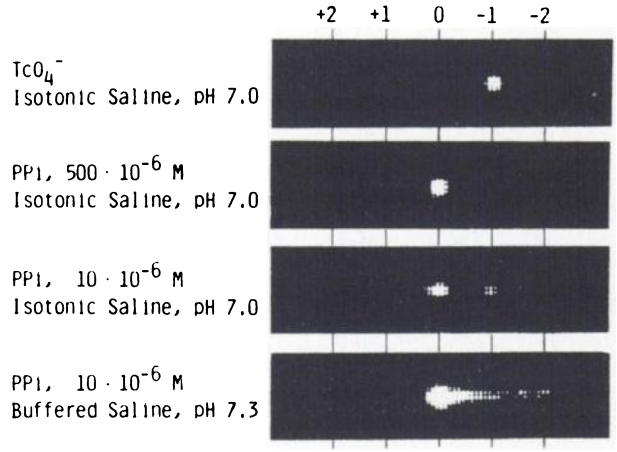


FIG. 3. Electrophoresis of Tc-99m PPi and pertechnetate was made in oxygen free environment. Activity was placed in middle of glass tube, heat circulation was prevented by purified sea sand. Constant temperature was thermostatically maintained in water bath. Movement of activity was observed by means of large field gamma camera.

very strong and is not broken down in vivo in the rat. By this experiment it is also shown, that the bone uptake as well as the urinary excretion of Tc-99m is identical for Tc-99m HEDP, MDP, and PPi, provided that no protein binding would occur (Fig. 2). The lower uptake in the bone and higher excretion in the urine of Tc-99m tripolyphosphate can be due to the presence of different species of Tc-99m phosphate complexes or to a consecutive in vivo breakdown of the complexes occurring in two stages (*17, 18*).

In summary, the current methods used for determining protein binding of Tc-99m-labeled phosphate compounds are unsatisfactory, but ammonium sulfate precipitation seems to be the most promising method. The protein bound fraction in the human plasma remains intact in vivo in the rat. Minimal protein binding, as expected, leads to better bone localization. Further work is needed to establish the different species of Tc-99m-labeled phosphate compounds present both in vitro and in vivo.

FOOTNOTES

* Laboratoire Banna, Genf.
† Byk-Mallinckrodt, Diefenbach-Sternberg, FRG.
‡ Benckiser-Knappsack, Ladenburg/Neckar, FRG.
‖ Centriflo dialysis Membrane Cones, type CF 256.

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ERRATUM

The publisher's information for the Book Review entitled *Diagnostic Imaging in Renal Disease (J Nucl Med* 21: 708, 1980) were inadvertently omitted. It should read: *Diagnostic Imaging in Renal Disease.* Arthur T. Rosenfield, Morton G. Glickman, and John Hudson. New York, Appleton-Century-Crofts, 1979, 332 pp, $33.50.