

INVESTIGATIVE NUCLEAR MEDICINE

Quantitative Lymphoscintigraphy I: Basic Concepts for Optimal Uptake of Radiocolloids in the Parasternal Lymph Nodes of Rabbits

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The activity-size distribution of radiocolloids has been studied using gel-chromatography scanning (GCS) of columns filled with Sepharose 4B gel. Rabbits were injected subcutaneously with the colloid of interest, laid supine beneath a gamma camera, and imaged every 15 sec for 2 to 4 hr. From the stored data, the uptakes in the parasternal lymph nodes were analyzed in terms of two-compartment model, and the rate constants measured. The substances tested were Au-198 colloid, Tc-99m antimony sulfide colloid, Tc-99m tin colloid, Tc-99m phytate, and Tc-99m sulfur colloid.

It was shown that the optimal particle size for the colloid is in the range 1–10 nm. The largest and most rapid uptake was found for Au-198 colloid, with a particle size of 5 nm, which appeared as a single peak in the GCS spectrum. The percentage uptake after 2 hr for Au-198 colloid was 8%, while it was 5% for antimony-sulfide colloid, which was the best of the Tc-99m-labeled colloids. The GCS spectrum for the antimony product showed a single-peaked size distribution with a somewhat broader range: 5–15 nm. The particles of the other colloids were either too large to pass into the lymphatic system, or too small to be trapped.

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The status of the lymphatic system is usually investigated by contrast lymphography. In this method a lymph vessel must be located, cannulated, and injected with contrast medium. In some cases, however, such a procedure cannot be used because of the lack of suitable lymph vessels. Thus it is not possible to examine the lymph flow from the primary tumor site of a malignant melanoma or in the parasternal lymphatics in breast carcinoma. Moreover, it is not possible to perform quantitative dynamic studies with this method. Some clinical contraindications also limit its use (1,2).

The search for complementary and alternative

methods has led to the use of a number of compounds labeled with radionuclides for lymphoscintigraphy. The earliest lymphoscintigraphic methods were based on Au-198 colloids (3–5). Although promising results were obtained, the absorbed dose at the injection site was unacceptably high, being of the order of 50–100 rad/ μ Ci (4,6). In the search for compounds offering better imaging properties for less absorbed radiation, substances labeled with Tc-99m have been explored (4,6–15).

Previous investigations have shown the usefulness of Tc-99m sulfur colloid (16) in visualizing the parasternal lymph nodes in rabbits (11–13,15). The method is applicable clinically (14), but comparison of the scintigraphic findings with those obtained from surgically removed nodes showed that almost 50% of the normal nodes failed to trap the sulfur colloid particles (17).

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Lately interest has shifted toward Tc-99m colloids with particles smaller than those of the sulfur colloid, and some of these have been tested clinically (4,6,7,9,10).

The aim of the present investigation, therefore, was to set up an experimental model for lymphoscintigraphic studies, in which the radiochemical and biokinetic characteristics of different compounds could be compared.

MATERIALS AND METHODS

Radiopharmaceuticals. Four different colloids labeled with Tc-99m were investigated: sulfur colloid ($^{99m}\text{Tc}_2\text{S}_7$) (16), tin colloid* [$^{99m}\text{Tc}(\text{Sn})\text{S}$], antimony sulfide colloid† ($^{99m}\text{TcSb}_2\text{S}_3$), and sodium (Sn) phytate‡. Au-198 colloid§ was also used because of its well-defined particle size (about 5 nm). Pertechnetate, red blood cells (18), and human serum albumin§ labeled with Tc-99m were also injected subcutaneously.

Activity size distributions. The activity-size distributions of the various preparations were investigated using the technique of scanning a gel chromatography column, as previously reported (19,20). The special technique used to investigate colloids has been described in detail elsewhere (21,22), but briefly is as follows.

The sample to be analyzed is applied in a volume of 0.1 ml to the top of a column filled with Sepharose 4B gel and developed with 10 ml of 0.9% NaCl solution. The column is scanned with a NaI(Tl) detector collimated by a 1-mm slit, with the scanning profile recorded both digitally and on a strip-chart recorder. The count rate per centimeter of column length is then normalized to the total count rate from the column. In Fig. 1 the results obtainable with this technique are shown schematically.

The formation of Tc-99m phytate colloid in the interstitial fluid was simulated by mixing Tc-99m phytate with whole blood. The blood was then centrifuged and a 0.1-ml sample taken from the plasma for the GCS analysis.

Biological model. Experiments were performed on 23 rabbits weighting 1.5 to 2.9 kg. They were initially anesthetized with less than 30 mg/kg of pentobarbitone sodium¶ i.v. and were subsequently given about 3 mg/kg per hr to keep them still. The rabbits were fixed in a supine position in a specially made holder (Fig. 2A). A continuous infusion of about 10 ml/hr GLYKOS** was given through a cannulated ear vein. This particular biological model was chosen because dynamic studies could be carried out and also because a reproducible lymph flow could be established. The latter was important because uncontrolled movements were avoided and the respiratory movements of the chest gave the same passive contractility to the lymph vessels in all the experiments. Furthermore, continuous hydration could easily be administered.

The colloid (0.5 ml) was injected subcutaneously bi-

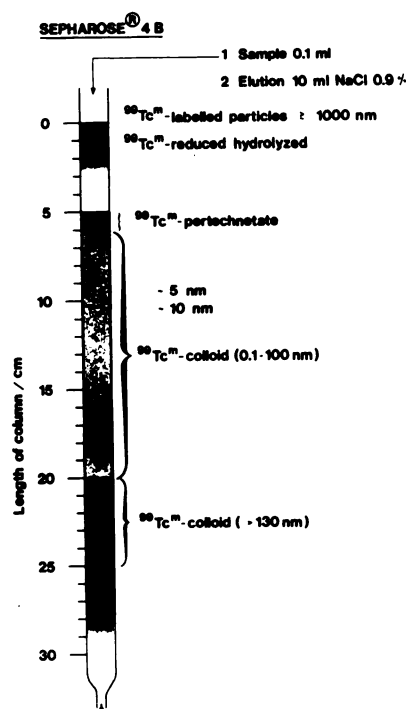


FIG. 1. Activity-size distributions obtainable with GCS technique on columns filled with Sepharose 4B.

laterally just below the xiphoid process. To increase re-sorption it was mixed with 100 IU hyaluronidase†† (4,11-15). The injections were given in several directions on each side, and were performed about 30 min after induction of anesthesia, when the decrease in lymph flow due to anesthesia is small (23-25). Images were made with a scintillation camera equipped with a parallel 16,000 hole collimator every 15 sec after the injection for 2 to 4 hr, the data being stored on magnetic tape. In some cases, the study was extended up to 7 hr. Regions of interest (ROI) including the lymph nodes were selected and time-activity curves generated. Typical activity distribution in a rabbit is shown in Fig. 2B, and the corresponding uptake curve for Au-198 colloid is seen in Fig. 2C.

Computer analysis. Background subtraction (see Fig. 2B) and correction for the physical decay of Tc-99m were performed on the time-activity curves with a computer. On the assumption that the depth of the lymph nodes in the supine rabbit is 7 mm, the calibration factor α for the scintillation camera (17) was estimated to be 4.2 cps/ μCi for Tc-99m, and 2.2 cps/ μCi for Au-198. The activity content of the lymph nodes could then be expressed as a percentage of the activity administered. If $A(o)$ is the activity injected and $N(t)$ the net number of counts in the ROI, then the percentage uptake in the nodes, $P(t)$, is given

$$P(t) = \frac{N(t) \cdot 100 \cdot e^{\lambda t}}{A(o) \cdot \alpha \cdot \tau} \quad (1)$$

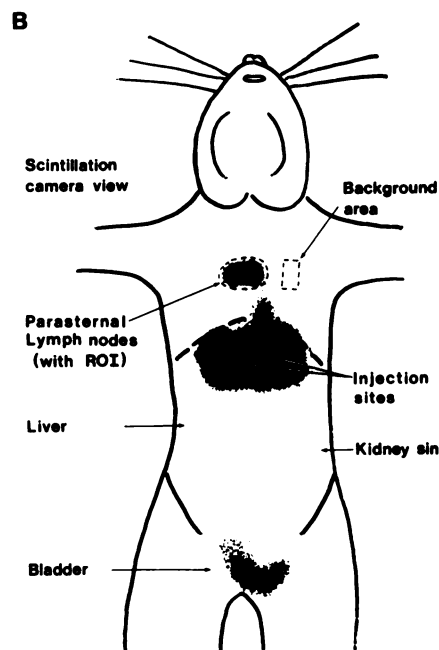
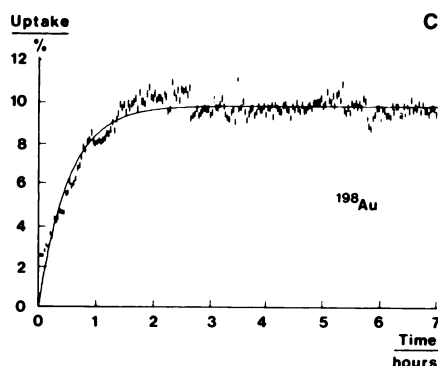
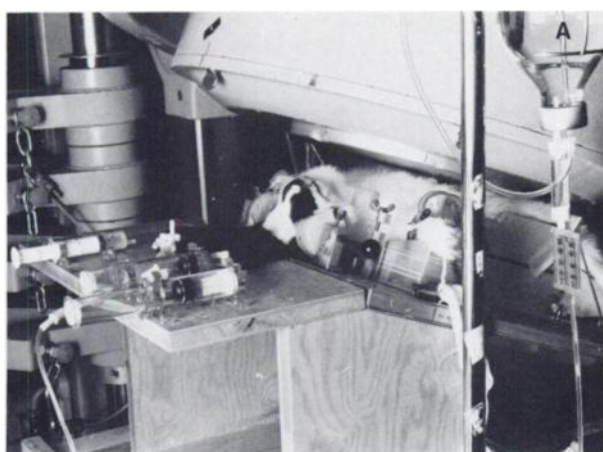


FIG. 2. Biological model used to register uptake in parasternal lymph nodes of rabbits. (A) Experimental setup with scintillation camera. (B) Image of activity distribution. Region of interest (ROI) is indicated. (C) Time-activity curve for the Au-198 colloid. Solid line shows result of fitting a two-compartment model to experimental points.

where t is the time after injection, τ is the frame time, and λ the physical decay constant for Tc-99m.

To estimate the flow rate of the colloid into the lymph nodes, the open two-compartment model shown in Table 1 was used. With the symbols in the figure, the rate of change of the colloid in the bolus, B , at the injection site, and in lymph node, L , with time t , can be written:

$$\frac{dB}{dt} = -B \cdot (k_1 + k_2) \quad (2)$$

$$\frac{dL}{dt} = B \cdot k_1 \quad (3)$$

$L(t)$, can thus be expressed by the equation:

$$L(t) = \frac{100k_1}{k_1 + k_2} [1 - e^{-(k_1 + k_2)t}] \quad (4)$$

In this model, the rate constant k_1 represents the uptake to the parasternal lymph nodes, and rate constant k_2 indicates the disappearance from the injection site to other parts of the body. These rate constants were evaluated for every experiment performed by fitting Eq. 4 to the experimental points (26).

RESULTS

The percentage of colloid transported to the lymph node,

Particle activity size distribution. The scan profiles

TABLE 1. RATE CONSTANTS FOR THE COLLOIDS STUDIED

Radiopharmaceutical	Rate constants		% lymph node uptake at			
	k_1 (sec^{-1})	k_2 (sec^{-1})	0.5 hr	1 hr	2 hr	4 hr
^{198}Au colloid	$(0.38 \pm 0.22)10^{-4}$	$(0.37 \pm 0.18)10^{-3}$	4.6	6.8	8.4	9.0
^{99m}Tc Sb_2S_3 colloid	$(0.31 \pm 0.18)10^{-4}$	$(0.50 \pm 0.06)10^{-3}$	3.5	4.7	5.3	5.4
$^{99m}\text{Tc}_2\text{S}_7$ (KReO_4) colloid	$(0.24 \pm 0.04)10^{-5}$	$(0.37 \pm 0.09)10^{-3}$	0.3	0.4	0.5	0.5
$^{99m}\text{Tc}(\text{Sn})\text{S}$ colloid	$(0.31 \pm 0.43)10^{-5}$	$(0.23 \pm 0.17)10^{-3}$	0.4	0.6	0.9	1.1
^{99m}Tc phytate	$(0.10 \pm 0.09)10^{-4}$	$(0.32 \pm 0.34)10^{-2}$	0.4	0.5	0.6	0.6

TABLE 2. ACTIVITY-SIZE DISTRIBUTIONS FROM THE GCS PROFILES

Radiopharmaceutical	% Activity in various zones (cm)					Median activity distance (cm)
	0-3*	4-6†	7-14‡	15-19	20-25§	
¹⁹⁸ Au colloid	1.3	5.9	89.8	2.7	<1	9.5
^{99m} TcSb ₂ S ₃ colloid	4.9	16.9	66.8	9.8	1.3	10.2
^{99m} Tc ₂ S ₇ (KReO ₄) colloid	11.7	4.5	12.8	14.1	56.5	20.2
^{99m} Tc(Sn)S colloid	7.5	6.9	59.3	13.9	10.5	11.0
^{99m} Tc phytate	7.9	35.7	55.1	2.2	<<1	7.2
^{99m} Tc ₂ S ₇ (no KReO ₄)	40.4	12.0	12.4	8.3	27.0	8.3
^{99m} Tc HSA	25.7	15.5	55.4	1.1	2.2	7.4

* Reduced hydrolyzed ionic Tc.

† Pertechnetate.

‡ Colloid size 5-50 nm.

|| Colloid size 50-100 nm.

§ Colloid size > 130 nm, void volume.

showing the activity-size distributions for the different radiopharmaceuticals are given in Figs. 3A and B, and in Table 2 the main characteristics are listed.

Au-198 colloid with well-defined particle size of 5 nm, is found to have an activity peak 95 mm from the top of the column. The profile is almost Gaussian, with a minor deviation indicating that about 3% of the activity has somewhat larger particle size.

Antimony sulfide colloid migrates a little farther due to its greater particle size: about 5-15 nm (6,10,27). The peak activity appears at 100 mm and the distribution is broadened due to particles with larger size. At 55 mm a peak is obtained, indicating that about 10% of the activity is present as free pertechnetate.

The large particles in the sulfur colloid [400-1000 nm (16)] migrate through the column together with the front of the eluent, and some 65% of the activity is found at about 210 mm from the top. From the distribution, it can also be seen that at 60 mm about 2% of the activity is due to free pertechnetate. The remaining activity gives a broad distribution with most of the activity attributed to small particles, found at 85 mm in the column.

Tin colloid shows a broad particle-size distribution, with large particles. The activity distribution in the column is similar to that for both the sulfur colloid and the antimony sulfide colloid. About 80% of the activity has the same activity-size distribution as the antimony sulfide colloid, the remaining activity apparently being due to much larger particles.

The smallest particle-size distribution was shown by the Tc-99m phytate colloid. The results from the Sepharose 4B column scanning show that the particles are less than 5 nm. About 90% of the activity is found within these particles. The same activity-size distribution was obtained when the supernatant containing the red blood cells was analyzed. About 20% of the total activity remained within this fraction.

When the KReO₄ was excluded in the preparation of the Tc-99m sulfur colloid and the boiling time reduced from 3 min to 1, the activity-size distribution was dramatically changed, the particles being much smaller. Only about 30% of the activity was now attributed to the larger particles, whereas 20% was found with smaller particle size.

Tc-99m human serum albumin contains both smaller-sized particles, reminiscent of the phytate distribution, and larger particles like those of the sulfur colloid. In the former part of the distribution, 60% of the activity is found, in the latter, 3%.

Time-activity curves. The time-activity curves in Figs. 2C and 4 show the percentage uptake in the parasternal lymph nodes for the five colloids investigated. In these curves, corrections have been made for background activity, physical half-life, and tissue attenuation. The vertical line for each reading gives the statistical uncertainty as s.d. The different curves represent typical results from all the experiments with the colloids. All show a similar pattern. Uptake in the lymph nodes starts immediately after the injection, a plateau in the uptake being reached for all the preparations after about 2 hr. The uptake varies somewhat, fluctuations in the first 2 hr indicating variations in lymph flow due to active muscle contractions. The highest uptake values are shown by the gold colloid (about 9% of the injected activity, Fig. 2C) followed by the antimony sulfide colloid (about 5%). Much lower values were obtained for the other preparations.

COMPARTMENTAL ANALYSIS

The difficulty in interpreting the time-activity curves objectively—because of their different shapes and because the experiments took different periods of time—was partly overcome by the compartmental analysis. In

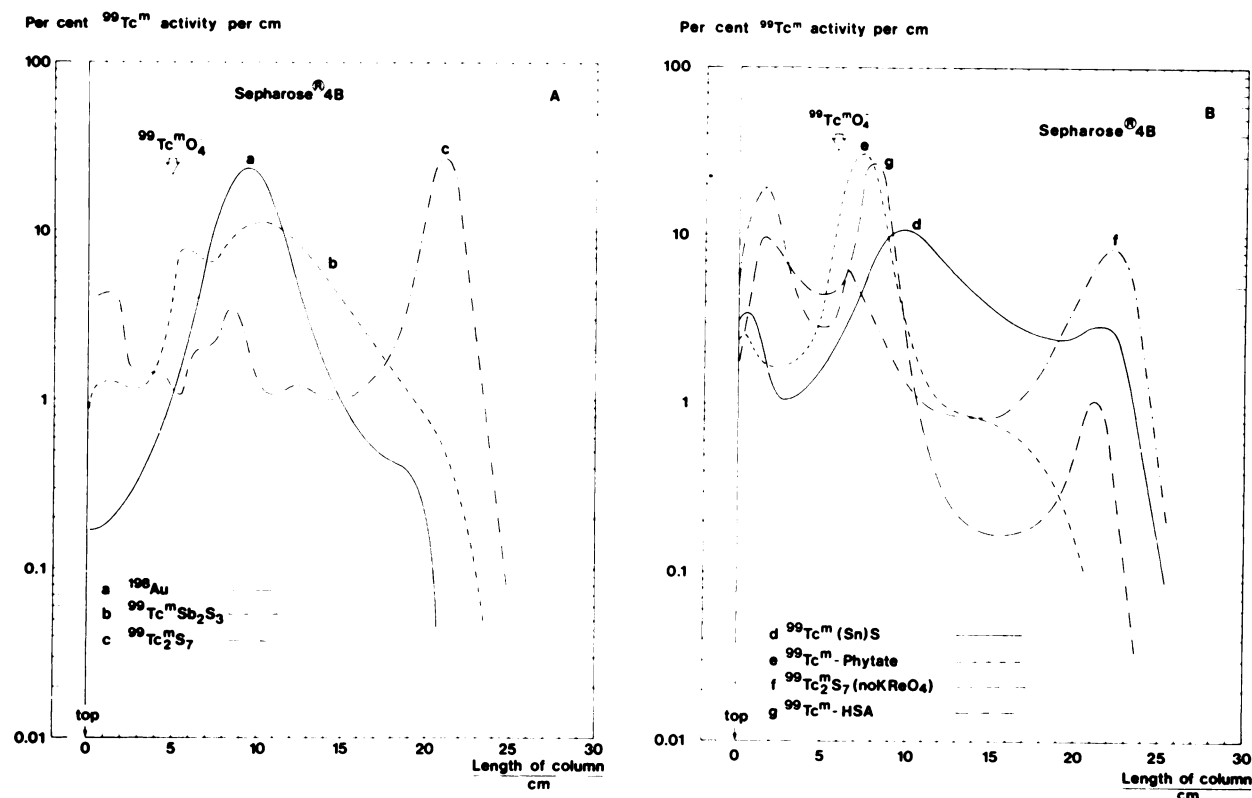


FIG. 3. Activity-size distributions obtained using GCS technique on Sepharose 4B columns. (A) Small-, medium-, and large-particle spectra for Au-198, ^{99m}Tc antimony sulfide, and ^{99m}Tc sulfur colloid, respectively. (B) Spectra obtained for ^{99m}Tc tin colloid, ^{99m}Tc phytate, ^{99m}Tc sulfur colloid without perrhenate, and ^{99m}Tc human serum albumin.

Figs. 2C and 4, the solid lines show the results of this analysis, and in Table 1 the values for the rate constants are given. The k_2 constant has a very narrow range, namely $(2-7)10^{-4} \text{ sec}^{-1}$ for almost all of the experiments. For the k_1 constant, the range is much greater: $(0.01-5)10^{-5} \text{ sec}^{-1}$.

The following results are valid for the different colloids: Au-198. Here the highest k_1 rate constants were found. In the images of the rabbits, no activity was observed in any part of the body except the lymph nodes at any time after the injection.

$^{99m}\text{TcSb}_2\text{S}_3$ showed some slight escape of the activity to other organs, such as liver, spleen, kidneys, and bladder. In one of the experiments, however, in which, by accident, part of the activity was introduced into the blood, the activities in these other organs were much enhanced and the value of k_2 increased by a factor of 2. These k values were excluded in obtaining the mean values in Table 1.

The results from ^{99m}Tc phytate showed the greatest spread in the values of the rate constants. The high values for k_2 can be accounted for by the observation of high activities in liver, kidneys, and bladder. Four hours after the injection, about 1% of the activity is found in the kidneys, 6% in the bladder, and 2% in the liver.

$^{99m}\text{Tc}(\text{Sn})\text{S}$ showed an irregular behavior, with scattered results.

$^{99m}\text{Tc}_2\text{S}_7$ gave the lowest uptakes, and in one experiment, in which the injection technique was different, the extralymphatic uptakes were increased significantly, giving a much larger k_2 . When the preparation procedure was modified to reduce particle size (see above), the k_1 constant increased by a factor of 6.

The k_1 and k_2 values for the Tc- 99m -labeled human serum albumin lie in the same range as the corresponding values for phytate. When Tc- 99m -labeled red blood cells were injected, very low values of both k_1 and k_2 were found, which reflects the difficulty experienced by red cells in leaving the site of injection. Nevertheless, some of them do reach the regional nodes, because a red cell, in spite of its $8\text{-}\mu\text{m}$ diameter, can enter a lymphatic capillary when it makes contact with the capillary wall.

PERCENTAGE UPTAKE

From the above time-activity curves and the compartmental analysis, the percentage uptake in the parasternal lymph nodes was calculated for various times after the injection. In Fig. 5 these uptake values for the radiocolloids after 0.5, 1, 3, and 4 hr are shown, the values being averages for all experiments performed. The accumulated activity in the lymph nodes at 4 hr is twice the activity at 30 min for all preparations. The uptake

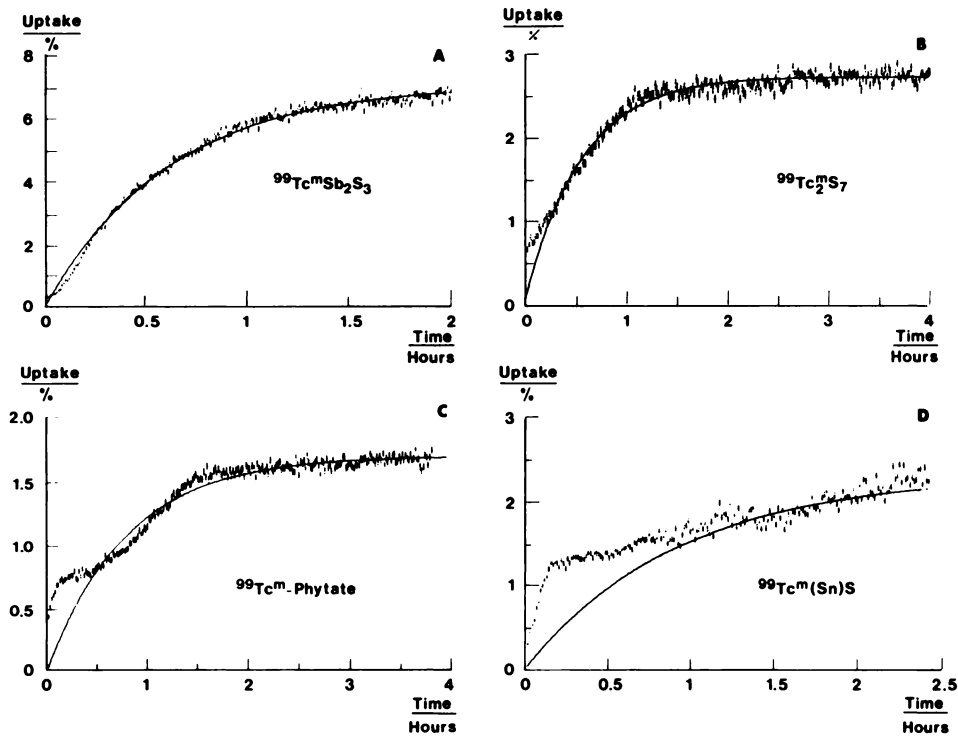


FIG. 4. Time-activity curves obtained for four of Tc-99m colloids investigated. (A) Antimony sulfide colloid, (B) sulfur colloid without perrhenate, (C) phytate, and (D) tin colloid. Curves show variations in uptake rate. Results of two-compartment analysis are shown by solid lines. Note differences in time scales.

is largest during the first 2 hr, the increase thereafter being small. At 4 hr, the uptakes for the different preparations lie between 0.5% and 9%, the highest being for Au-198 colloid.

CORRELATION BETWEEN ACTIVITY-SIZE DISTRIBUTION AND UPTAKE

From the activity profiles of the Sepharose 4B col-

umns, the mean activity-size distance in the column was calculated. This is the distance from the top of the column within which 50% of the activity is trapped. The values are given in Table 2. In Fig. 6, the percentage uptake 2 hr after injection is plotted as a function of this distance for the different preparations. The plot shows that there is a relationship between the uptake in the lymph nodes and the mean activity-size distance. The highest uptake values are registered with the Au-198

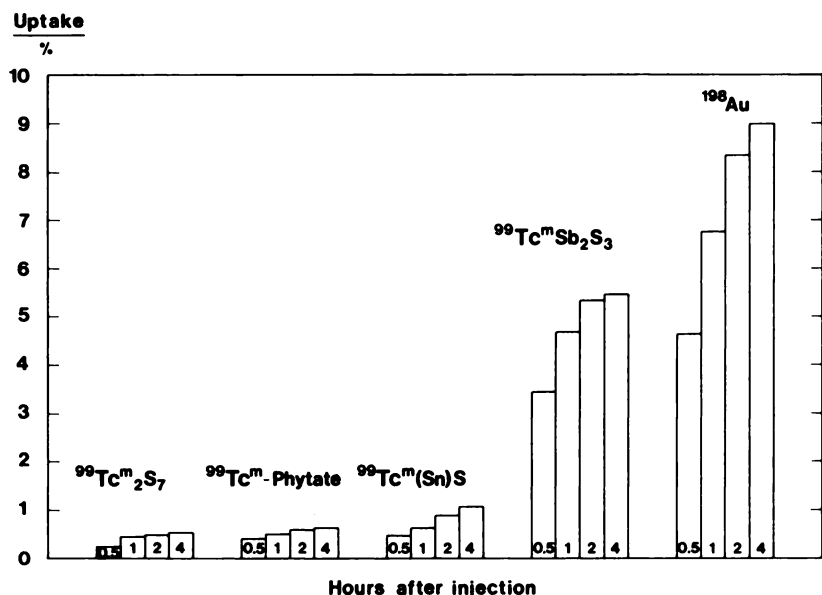


FIG. 5. Percentage uptakes in parasternal lymph nodes at different times after subcutaneous injection.

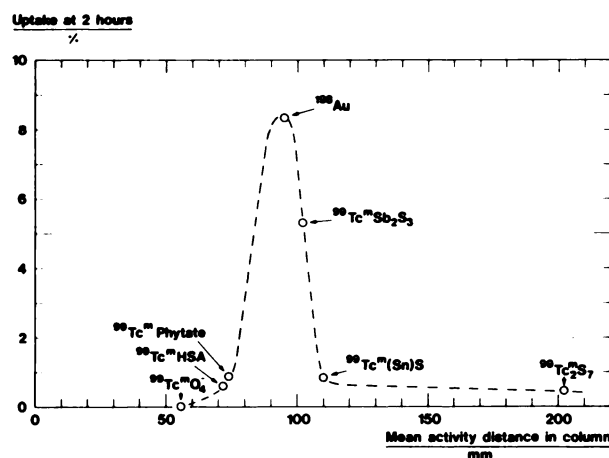


FIG. 6. Percentage uptake at 2 hr after injection, as function of mean activity-size distance in column, for seven compounds investigated.

colloid, whereas both larger and smaller complexes reduced the uptake. Antimony sulfide colloids, which have a particle-size distribution slightly larger than the Au-198 colloid, show only ~60% of the Au-198 uptake.

DISCUSSION

The differing behavior of these colloids is understandable when we consider the histophysiological characteristics of the lymphatic system and the dynamics of the blood capillaries and the interstitial fluid (28–30).

Lymph flow is affected by active and passive contractilities of the lymphatic walls and lymph nodes (4,28). Passive contractility is due to respiratory movements, rhythmic changes in the volume of the intestines, and movement of the limbs and other skeletal muscles. Active contractility is due to the intrinsic contractions of the smooth muscle in the walls of the lymphatics and lymph nodes (31). The increase in lymph flow due to movements of the muscles has been shown to lie between 1.2 and 4 times the lymph flow at rest (23,24,32). In addition, anesthesia retards lymph flow, the reduction being 40% within the first 2 hr after induction and 50% within 4 to 6 hr (24,25). The anesthetic has, however, a continuous effect on the flow, in contrast to the discrete effects given by the movement of the muscles. Hydration also affects lymph flow: increased hydration increases the flow and vice versa (28).

For the Au-198 colloid, with a well-defined particle size of about 5 nm, the highest percentage uptake of the activity was recorded. Also, the rate constant k_1 shows the highest value among the colloids investigated. The rapid transport of the gold colloid into the lymph is due to its ideal particle size, which enables it to pass through the lymphatic capillary pores and prevents it from passing through the pores of the blood capillary mem-

brane. This is also indicated by the relatively small value of the k_2 rate constant and by the fact that there is no evidence of uptake in other parts of the body. The antimony sulfide colloid shows a broader activity-size distribution in the GCS profile due to its size range of 5–15 nm. The largest particles are obviously too big to pass through the lymphatic capillary pores. A minor part of the activity consists of free pertechnetate, with molecular weight of 163, and of Tc-99m complexes with ligands of low molecular weight. These small-molecule compounds can to a considerable degree pass through the pores of the blood capillaries, which might explain the somewhat higher k_2 values as compared with those for Au-198. The minimum uptake of the Tc-99m sulfur colloid can be attributed to its very large particle size of 600 nm. In the scanning profile there is evidence of smaller particles at ~10 nm. It is obviously the latter fraction that contributes to most of the uptake in the lymph nodes. The larger particles are trapped in the interstitial fluid and are incapable of moving into any capillary. This is reflected in the very low value of the k_1 rate constant and almost the same value of k_2 as for Au-198.

In the scanning profile of the tin colloid, a relatively large part of the activity is carried in small particles, but the uptake in the lymph nodes is small. Further investigations are needed to explain this paradox. Possibly the pores in the lymph capillaries may be blocked by intermediate-sized particles. In addition, the local high concentration of large particles will change the colloid osmotic pressure, which might further reduce the inflow to the lymph vessel. The k_1 values obtained are very small whereas the k_2 values are of the same order as above.

The ^{99m}Tc phytate particles are of about the size of albumin molecules or a little less. Thus the permeability of the blood capillary pores becomes significant, and an exchange of the particles with blood takes place. Much of the activity is also found in other organs, the uptake coming very shortly after the injection. This relatively high outflow of activity is reflected by the larger value of the k_2 rate constant as compared with those of the other colloids.

When only pertechnetate was injected, the activity was soon found in the general circulation and uptake was registered in the thyroid. No activity was registered in the lymph nodes. This observation supports the theory of transport through the blood capillaries. Further evidence for this transport was shown using Tc-99m-labeled human serum albumin, in which case activity appeared both in the kidneys and the bladder. Its disappearance from the injection site was much slower because of its lower permeability.

CONCLUSION

It is obvious that there is a very narrow size range that permits particles to migrate into the lymph while re-

stricting passage into the blood. Figure 6 shows that for maximum uptake in the lymph nodes the particle size must be such as to give a migration distance of ~90 mm in the Sepharose 4B-column. In the discussion we accounted for this by postulating the existence of a particle-size window with which optimal conditions for lymphoscintigraphy with subcutaneous injection are obtained.

The most suitable colloid for use in lymphoscintigraphy with subcutaneous injection is shown to be one with a very small range of particle sizes, of the order of a few nanometers.

Our previous studies of patients with breast cancer have shown poor correlation between the uptake of Tc-99m sulfur colloid in the parasternal lymph nodes and histopathological findings for the nodes (17). In a current study of patients with malignant melanoma, however, preliminary results with antimony sulfide colloid indicate a better correlation (22).

FOOTNOTES

* Tc-99m Lymphoscint, Solco, Solco Nuclear, Basle, Switzerland.

† Labelaid DRN 4333 Philips, Duphar, B.V. Petten, Holland.

‡ Solco Phytate, Solco Nuclear, Basle, Switzerland.

§ Au-198 colloid, The Radiochemical Centre, Amersham, England.

¶ Tc-99m human serum albumin, New England Nuclear Corp., Boston, MA.

† Mebumalnatrimum, ACO, Sweden.

** Invertos, (0.1 g/ml Glykos) ACO, Sweden.

†† Hyalas, LEO, Sweden.

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