Lymphoscintigraphy with Tc-99m-Labeled Dextran

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Current agents for lymphoscintigraphy have limitations because of slow migration of the colloidal tracers from the injection site and the unknown effect of phagocytosis on the removal of the labeled particles. The usefulness of Tc-99m dextran (TcDx) with a molecular weight of 110,000 has been tested for lymphoscintigraphy. Computer-assisted dynamic imaging and serial blood sampling in 13 dog experiments demonstrated that the tracer cleared only by lymph drainage from an interstitial injection site. Following interdigital injection of 1.0 ml (0.5–5.0 mCi), TcDx reached the knee or elbow lymph nodes in 12.4 ± 6.5 (1 s.d.) sec, and the inguinal or axillary lymph nodes in 98.0 ± 42.3 sec. It cleared from the injection site with a half-time of 31.5 min. In a dog with surgically induced lymphedema, tracer migration was markedly delayed in the edematous leg and the radionuclide lymphoscintigram resembled the contrast lymphangiogram. Initial studies in man yielded high-quality radionuclide lymphograms of the leg, and the pelvic and paraaortic lymph nodes. We conclude that TcDx is very promising for lymphoscintigraphy.

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The human lymphatic system is conventionally imaged for diagnostic purposes by contrast lymphangiography. However, standard ethiodol lymphangiography suffers from several acknowledged shortcomings, such as tedious cannulation of a lymph vessel, pulmonary oil emboli, hypersensitivity reactions to the iodine component of the contrast medium, failure to study lymph flow from a primary tumor site, and failure to perform kinetic physiologic and quantitative studies since the contrast medium is administered by a perfusion pump into the lymph vessel (*1*). Alternatively, a variety of radionuclide approaches and labeled agents have been examined to overcome these limitations (*1–9*). Perfusion lymphoscintigraphy with Tc-99m-labeled albumin was proposed to assess the need for a standard contrast lymphangiogram, which requires lymph-vessel cannulation (*1*). Au-198 colloids provided high-quality lymphoscintigrams after interstitial administration because of their optimum particle size, but their use was abandoned because of unacceptably high absorbed radiation at the injection site (*16*). Among the Tc-99m-labeled compounds proposed for lymphoscintigraphy—such as sulfur colloid, tin colloid, phytate, red blood cells, and albumin—only antimony sulfide colloid exhibited satisfactory properties for this purpose (*2,3,6–9*). This agent has been used in numerous studies for the evaluation of the lymphatic system in patients with breast carcinoma, truncus melanoma, and pelvic lymph-node metastases (*2,3,8*). Despite encouraging results, there are two major limitations to the use of Tc-99m colloids, due mainly to the particulate character of the tracers used: (a) tracer migration from an interstitial injection site is only 1–35% in 24 hr (*10*); and (b) clearance from the interstitial space and trapping of the colloidal particles is dependent on the particle size and on the functional state of the reticuloendothelial system (*6,9,11*), and thus does not reflect lymphatic flow. The latter may account for the reported finding that approximately 50% of normal parasternal lymph nodes failed to trap colloid activity and thus were not distinguishable from lymph nodes with metastases (*2*). A noncolloidal nonparticulate tracer

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compound, soluble in lymph fluid and with molecules large enough not to penetrate the capillary membrane after interstitial administration, would be a desirable substance for the purpose of lymphoscintigraphy.

Dextran, a polysaccharide used clinically as a plasma substitute, is known to remain in the vascular space after intravenous administration. Accordingly, this substance should clear from the injection site only by lymph drainage after interstitial administration (*12,13*). We recently succeeded in labeling dextran with Tc-99m with excellent in vivo and in vitro stability, and documented its potential use for radionuclide angiocardiography in animal experiments (*14*). It was the purpose of the present study to examine the potential value of Tc-99m dextran for lymphoscintigraphy.

METHODS

Radiopharmaceutical preparation. We have described our labeling procedure, as well as the purity and in vivo and in vitro stability of Tc-99m dextran (*14*). Briefly, Tc-99m is attached to dextran using stannous ion reduction of pertechnetate. One gram dextran is dissolved in 10 ml of 0.9% saline solution and deoxygenated by purging with nitrogen gas at 50 ml per min for 1 hr; it is then mixed with 1.5 mg of $SnCl_2$ dissolved in 50 μl of concentrated HCl. Under aseptic conditions, 1.0-ml aliquots of this stannous-dextran solution is then dispensed through a sterile 0.22-μm membrane filter into 5-ml sterile vials, which are stoppered and sealed in a nitrogen atmosphere. Stannous-dextran kits can be stored at 2–4°C for several weeks, thus facilitating routine use. Before a study, freshly eluted pertechnetate is added to the vial, mixed, and left at room temperature for 5 min. Dextran with a mean molecular weight of 110,000* was used in order to avoid regional blood-capillary uptake and washout from the injection site, since it is known that dextran with a molecular weight less than 40,000 does penetrate capillary membranes (*12*). Sterility and nonpyrogeneity were assured by randomly testing one of the ten kits in each batch.

Imaging. The suitability of Tc-99m dextran for lymphoscintigraphy was tested in 15 mongrel dogs weighing from 25–31 kg and anesthetized with pentobarbital (25 mg/kg). In eight dogs, 1.0 ml of Tc-99m dextran (0.5 mCi) was injected through an infusion set interdigitally and subcutaneously in either the front limb (4 dogs) or the hind limb (4 dogs). Sequential gamma imaging‡ was performed over the injection site at 10-min intervals for 2 hr. A region of interest was drawn over the dog's paw for calculation of the clearance rate from the injection site. In five dogs the times of tracer migration to the knee (or elbow) and groin (or axillary) areas were also measured using a large-field-of-view camera. Serial analog images were obtained at 5-sec intervals after interdigital injection of 1.0 ml dextran labeled with 5.0 mCi of Tc-99m. In addition, venous blood was sampled in one-min intervals to estimate the appearance rate of the tracer in the blood. For comparison, the appearance characteristics of activity in venous blood was also measured after subcutaneous interdigital injection of 1.0 ml (0.5 mCi) of pertechnetate in one dog. In order to compare contrast with lymphoscintigraphy, lymphedema was induced surgically in one dog by obstructing lymph nodes and lymph vessels in the right groin. One month after surgery a lymphedema developed in the right leg, at which time a contrast ethiodiol lymphangiogram was obtained by cannulation of a lymph vessel, and a lymphoscintigram by subcutaneous injection of 1.0 ml (0.5 mCi) Tc-99m dextran. To provide controls, both hind limbs were similarly treated.

At the end of each study, camera views of the thyroid gland and the stomach were obtained in search of released Tc-99m.

Finally, initial studies in man were performed. Multiple camera views of the left leg, the groin, the pelvis, and the abdomen were obtained 45 min after interdigital injection in the foot of 0.5 mCi (0.5 ml) of Tc-99m dextran.

All mean values are given with one standard deviation.

RESULTS

Interstitial administration of Tc-99m dextran resulted in high-quality lymphoscintigrams, as shown by examples for the hind leg (Fig. 1), for the front leg (Fig. 2), and for the knee areas (Fig. 3). The main lymph vessel of the legs, the pelvis, and the knee are well visualized, together with their respective lymph nodes and the smaller lymph vessels of the dog's paw. In all five experiments Tc-99m dextran migrated in the lymph vessels relatively fast: it reached the lymph nodes of the knee or elbow within an average time period of 12.4 ± 6.5 sec, and the inguinal or axillary lymph nodes in 98.0 ± 42.3 sec. The tracer cleared from the injection site monoexponentially within the first hour with a half-time of 31.5 min (Fig. 4). Serial blood sampling revealed entrance of the tracer activity into the venous blood stream in an S-shaped time-activity curve with maximum slope between 4 and 10 min. This is considerably later than free pertechnetate, as shown in Fig. 5. In the dog with surgically induced lymphedema in the right leg, tracer migration was markedly slower on the right side than on the left, where a normal migration pattern was noted, placing activity in the inguinal areas after 10–30 sec. The left pelvic lymph nodes were visualized faintly at 60 sec and became more prominent during the following hour. In contrast, even one hr after tracer administration the right pelvic lymph system did not demonstrate any appreciable uptake (Fig. 6, left). On the contrast lymphograms in the same dog (Fig. 6, right), the flow pat-

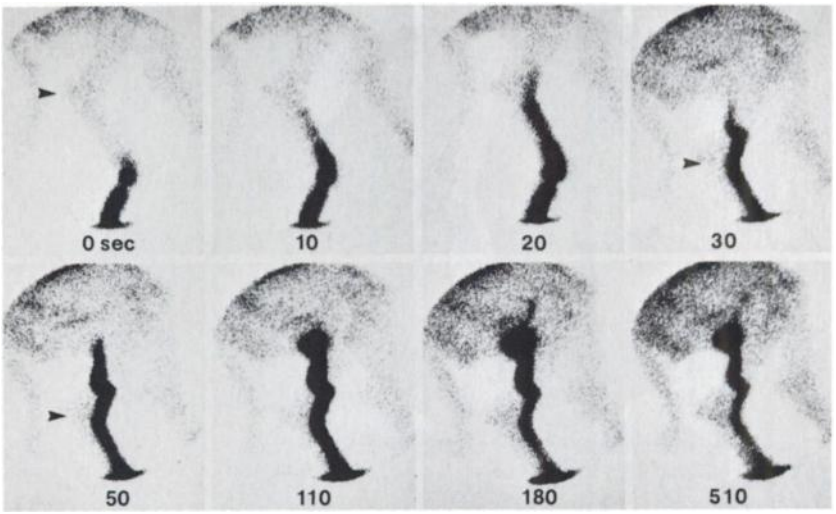

FIG. 1. Serial lymphoscintigram of dog's right hind limb obtained after interdigital subcutaneous injection of 1.0 ml (5 mCi) of Tc-99m-labeled dextran with molecular weight 110,000. In this experiment, tracer reaches knee area (arrow) in ~20 sec, and inguinal lymph nodes in ~110 sec.

tern was normal on the left side, whereas marked collateralization was present on the right. However, because of the pressure infusion, the contrast medium did accumulate in the right-sided pelvic lymph nodes.

In man, high-contrast lymphoscintigrams were obtained with Tc-99m dextran, as shown in Fig. 7. Forty-five min after interdigital injection, a continuous tracer stream through the lymph vessels and lymph nodes allowed multiple camera views to visualize the calf, thigh, groin, pelvis, and abdominal lymph system. Consistent with the fate of Tc-99m dextran after entering the blood steam, liver and kidneys are faintly visualized and the low-molecular-weight dextran had accumulated in the urinary bladder.

None of the studies with labeled dextran revealed uptake of activity in the thyroid or the stomach. There was also no evidence of bone-marrow uptake.

DISCUSSION

These results demonstrate the utility of Tc-99m-labeled dextran as an agent for lymphoscintigraphy. Any agent for this purpose must be examined for three criteria: (a) molecular size, (b) physical and biological distribution in the interstitial space, and (c) possible problems related to the labeling with a radionuclide.

Molecular size. The chemical properties and the pharmacokinetics of dextran's polysaccharide molecule are almost ideal for the purpose of lymphoscintigraphy. Its molecular size can be selected in advance to be large enough not to penetrate the capillary membranes and to remain within the interstitial space. Garlick et al. (*15*) reported a sharp reduction in membrane penetration for molecules larger than 4–5 nm in radius. With respect to dextran, this implies that molecules with a molecular weight larger than 40,000 should not penetrate blood capillary membranes because this molecular size represents an Einstein-Stokes sphere of ~4.5 nm radius. Consistent with this are observations that dextran molecules smaller than 40,000 Dalton are subject to glomerular filtration and urinary excretion (*17*). Using interstitial microinjections of fluorescein-labeled dextran in rabbits, Rutili et al. (*12*) demonstrated that the transport of dextran molecules larger than 37,000 from the interstitial space is due to lymphatic drainage alone. This supports the conclusion that the permeability of the blood capillary membrane for dextran is the same in both directions. Parallel to our work, fluorescein-labeled dextran was recently successfully used for fluoroescence microlymphography in man by Bollinger et al. (*13*). Thus, as opposed to the colloidal tracers commonly used, Tc-99m dextran offers a major advantage in that a

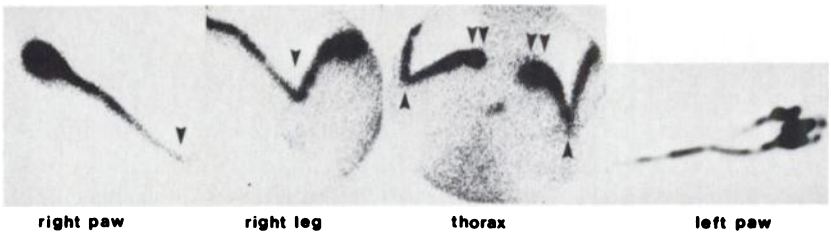

FIG. 2. Lymphoscintigrams of dog's front legs obtained 20 min after bilateral interdigital subcutaneous injection of 1.0 ml (0.5 mCi) of Tc-99m-labeled dextran. Main lymph vessels of both front legs are visualized up to axillary lymph nodes (double arrow). Single arrow indicates elbow. Lymphoscintigram of left paw was obtained after multiple interdigital injections and was digitized and background-subtracted. The smaller lymph vessels of dog's paw are well visualized. No activity is noted in thyroid gland.

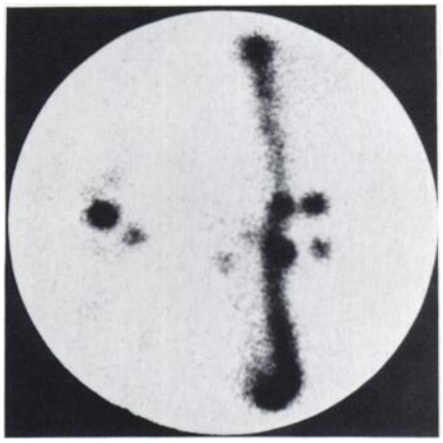

FIG. 3. Lymphoscintigram of the knee area of dog, obtained with pin-hole collimator 1 hr after bilateral interdigital injection of 1.0 ml (0.5 mCi) of Tc-99m-labeled dextran. This dog had surgically induced lymphedema on right side. In area of left knee, there is a well-visualized main lymph vessel with multiple lymph nodes, whereas on right side only two lymph nodes are visualized faintly. (Compare also Fig. 6.)

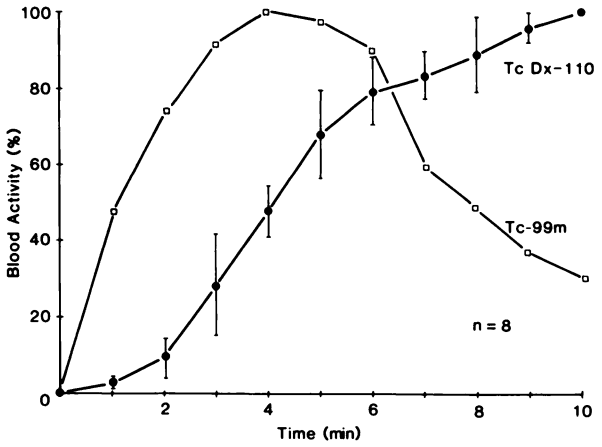

FIG. 5. Time-activity curves from blood after subcutaneous injection of Tc-99m-labeled dextran with molecular weight 110,000 (TcDx-110, closed circles) and free pertechnetate (open squares). Tc-99m-labeled dextran enters venous blood stream with a 4- to 10-min delay caused by lymphatic drainage. Activity was normalized, placing maximum blood activity at 100%.

well-defined molecular size can be selected for lymphoscintigraphy. For Au-189 colloid, with a relatively favorable and well-defined particle size of about 5 nm, good removal of the tracer from an interstitial injection site was measured by Strand et al. (*6*). However, the local radiation dose of 50–100 rads/μCi is too high for routine clinical use of this nuclide (*16*). Tc-99m sulfur colloid tracer consists of very large particles (50–600 nm) and shows only minimum clearance from the injection site and minimum uptake in regional lymph nodes. Strand et al. (*6*) demonstrated a better size distribution for antimony sulfide colloid (5–15 nm), consistent with a higher regional lymph-node uptake in their rabbit model. However, these authors believe that many TcSbS particles are still too large to enter the lymphatic capillaries. These size-related limitations of colloids result in a relatively slow and variable clearance from the injection site of only 1–35% in 24 hr (*10*), whereas Tc-99m dextran cleared uniformly in a monoexponential mode with a half-time of about ½ hr. We used dextran with a mean molecular weight of 110,000. Consistent with the pharmacokinetics discussed above, interstitial administration resulted in high-contrast lymphoscintigrams in both human and animal studies. Background activity rose only gradually with time and the appearance of activity in venous blood was characterized by an S-shaped time-activity curve, with a delayed onset relative to free pertechnetate, when both were injected interstitially. This delay of 2–4 min is explained by the drainage

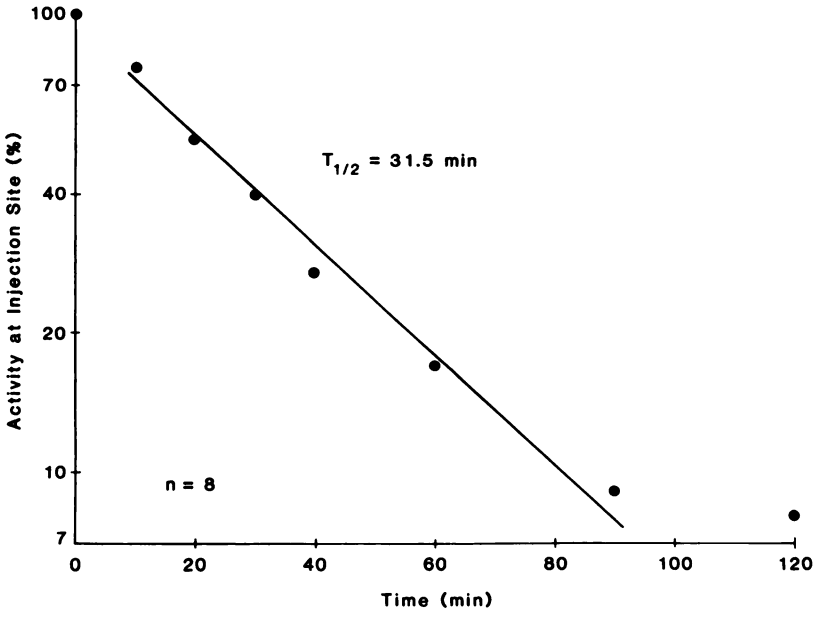

FIG. 4. Time-activity curve after subcutaneous injection of 0.5 ml of Tc-99m-labeled dextran, obtained from region of interest over injection site. Tracer clears in a monoexponential mode within 1 hr after injection, with clearance half-time of ~½ hr.

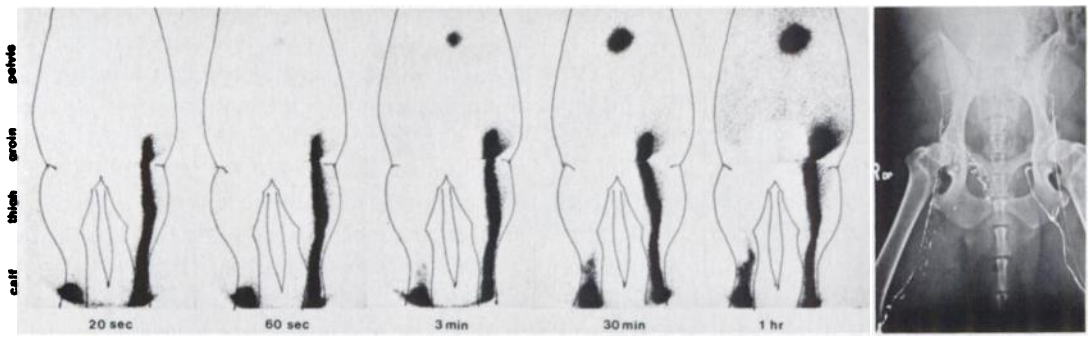

FIG. 6. Serial lymphoscintigrams of dog's lower extremities after bilateral interdigital injection of 1.0 ml (0.5 mCi) of Tc-99m-labeled dextran (left). This dog had surgically induced lymphedema in right leg. Note normal lymphoscintigram of left leg, with filling of left-sided pelvic lymph system, whereas tracer migration in right leg is markedly delayed and there is no uptake in right-sided pelvic lymph nodes. Contrast lymphogram of same dog (right). There is normal lymph flow on left side, with filling of left-sided pelvic lymph nodes. Right leg's lymphangiogram shows multiple collateralization and also visualization of right-sided pelvic lymph system by contrast medium. This difference from radionuclide lymphoscintigram might be explained by unphysiologic pressure in administration of contrast medium (see text).

of Tc-99m dextran from the interstitium and its subsequent collection in large lymph vessels with a slower flow than in the venous blood stream and, thus, a delayed entrance into the venous blood. From these studies, it cannot be excluded that a small amount of low-molecular-weight dextran (less than 40,000) did penetrate the blood capillary membranes and enter the blood stream directly, because dextran with a mean molecular weight of 110,000 contains some low-weight molecules (less than 40,000). This is consistent with results in preliminary patient studies using Tc-99m dextran with a mean molecular weight of 40,000. Only a very faint lymphoscintigram could be obtained, whereas background and urinary bladder activity rose rapidly. There was, however, no thyroid or stomach uptake (E. Henze, et al., unpublished data). In order to develop a reliable agent for clinical routine use, either dextran with the relatively high mean molecular weight (110,000) used in this study is required, or purified dextran of molecular weight between 40,000 and 70,000. From a practical point of view, the narrow range of molecular weights 40,000–70,000 is preferable because these dextrans are already in clinical use, whereas dextran 110,000 is not used in the United States. Thus, further kinetic studies are needed to evaluate the optimum fraction of dextran to be used for lymphoscintigraphy.

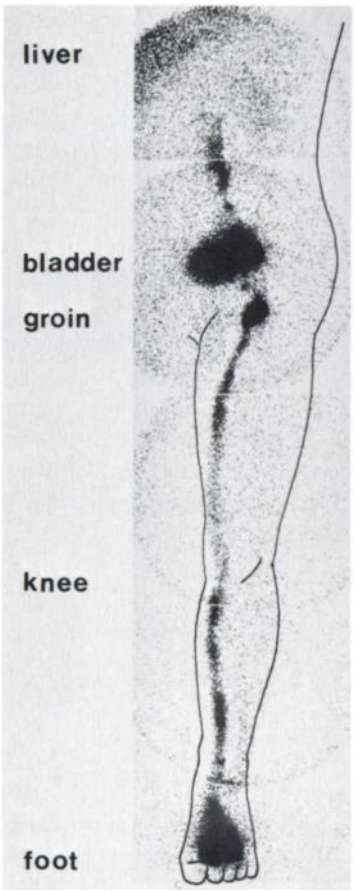

FIG. 7. Lymphoscintigram in man obtained 45–60 min after interdigital injection of 1.0 ml (0.5 mCi) of Tc-99m-labeled dextran. Lymph vessel of leg is well visualized, along with inguinal, pelvic, and para-aortic lymph nodes. As dextran slowly enters the blood stream, liver, kidney, and urinal bladder show uptake of activity.

Interstitial distribution. The biological and/or physical distribution in the interstitial space of a tracer to be used for lymphoscintigraphy is of great importance. Particles such as labeled colloids have certain appreciated disadvantages for this purpose. They are not soluble in the liquid compartment of the interstitium and they are thus subject to phagocytosis, mainly by macrophages. Their removal from an interstitial injection site, therefore does not necessarily reflect lymph flow but is largely dependent on the specific functional state of the macrophages (*6,9,11*), which seems to vary considerably with individual anatomic, physiologic, and pathologic factors that contribute to the rate of removal and dispersion of the colloidal tracer in an unpredictable manner (*10*). This may account for the failure to localize in normal mammary lymph nodes after epigastric administration,

leading to the low predictive accuracy as to whether the retrosternal lymph nodes were normal or affected by breast cancer metastases (*2*).

Dextran is water-soluble and is not bound to plasma or interstitial fluid proteins. Although dextran eventually becomes trapped by the reticuloendoendothelial system of the liver for oxidation as a foreign molecule (*17*), there is no evidence for phagocytosis of dextran in the interstitium (*12*). Therefore, labeled dextran will be distributed only in the liquid phase and will reflect only lymph flow in a physiologic mode. This may enable us to study regional and global lymphatic flow qualitatively and quantitatively. Initial evidence is shown in the dog study with surgically induced lymphedema. The edematous right leg demonstrated a marked (and measurable) delay, and no regional uptake in the right-sided pelvic lymph system was present. This pattern most likely reflects the true physiologic situation better than the contrast lymphangiogram, where the lymph vessel was cannulated and the contrast medium was administered with an unphysiologically high pressure. This may lead to the opening of collaterals and to the uptake of the right-sided pelvic lymph nodes.

The underlying mechanism of accumulation of labeled dextran in the lymph nodes (Figs. 6 and 7) is unknown at this time. Most likely the tracer remains in the fluid phase but more detailed autoradiographic examination is needed to define the internal distribution of Tc-99m dextran within the lymph nodes. Whether changes in the specific activity will affect the relative lymph-node uptake, and thus could be used to optimize deposition of the tracer in the nodes, awaits also further evaluation.

Labeling of dextran. The in vitro stability of Tc-99m dextran is excellent; so is the in vivo stability after i.v. administration (*14*). This study confirmed that there is no evidence for an appreciable amount of uncomplexed Tc-99m after interstitial injection. No thyroid or stomach uptake could be seen in patient or animal studies if the labeling procedure was performed properly. Preparation of the stannous-dextran kits is convenient, the kits can be kept stable and sterile for weeks, and the labeling procedure is very simple, reliable, and reproducible (*14*). The possible formation of Tc-99m stannous colloid needs to be addressed because of the solution of $SnCl_2$ in HCl and the pH of 3.6–4.0 in the final preparation. As demonstrated elsewhere, the formation of Tc-99m stannous colloids could be excluded by thin-layer chromatography and paper chromatography of freshly prepared Tc- 99m dextran (*14*). In vivo, colloids would be trapped mainly in the liver and bone marrow. If they are large enough not to penetrate the capillary membrane and result in good lymph scans, they should not be subject to urinary excretion. In our previously reported results (*14*) and in this study, no bone-marrow or prominent liver uptake was noted.

Clinical implications. Tc-99m dextran could become a useful agent for lymphoscintigraphy. It compares favorably with Tc-99m colloids and contrast lymphography. This agent reflects lymph flow from an injection site in a more physiologic manner and might be useful to trace lymph vessels and lymph nodes after local injection into an area of interest—for instance close to a breast cancer, or into the ischiorectal fossa for prostatic, rectal, or uterine cancer, or subcutaneously in patients with truncus melanoma. Further, it could be of value for staging Hodgkin's disease or other lymphomas. Serial quantitative and qualitative scans before and after surgery and/or radiation therapy are possible because the radiation dose is very low and injection can be performed repeatedly. This new agent may also be very helpful for differentiating primary or secondary lymphedema from edema caused by chronic venous disease, by measurement of regional lymphatic flow or clearance from the injection site.

Our initial experience with Tc-99m dextran in a limited number of patients is encouraging (see Fig. 7). Although the liver uptake could limit the quality of abdominal lymph scans, the ratio of cts/pixel in pelvic lymph nodes relative to liver was 11.5 to 1.52, and thus satisfactory for visualization of abdominal nodes. Further, there was no pain caused by the injection. Although adverse reactions after intravenous administration of dextran have been described, we have seen none to date in our patient studies. More experience is needed to determine whether subcutaneous injections of such small amounts as 50–100 mg per dose will cause any allergic reactions.

We conclude that Tc-99m dextran is a very promising agent for lymphoscintigraphy. Animal as well as pilot studies in man produced high-contrast images of the lymph system. For clinical use, the optimum molecular weight of dextran to be labeled, and its potential superiority over Tc-99m labeled colloids, needs to be established further. The potential value of this new radiopharmaceutical for diagnosis and followup of patients with cancer, lymphoma, and primary lymphatic disease awaits clinical trials.

FOOTNOTES

* Pharmacia Laboratories, Piscataway, New Jersey.

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