Fasted, sensitized rats were not capable of handling the fat load and hyperlipemia resulted. (6) The source of the cholesterol and lipid P in the hyperlipemic rats was the liver. (7) LM actively and immediately mobilized triglycerides from the depots and this action did not depend upon sensitization or fasting.

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## Effect of Specific Activity on Distribution of Radiolutecium ($Lu^{177}$).* (23353)

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In previous studies on effectiveness of radiolutecium ($Lu^{177}$) for irradiating lymph nodes in the dog, the possibilities of this rare earth were demonstrated(1,2). Certain difficulties, however, greatly limited the effectiveness of the isotope. With both tracer and therapeutic amounts, irradiation was selectively delivered to the regional lymph nodes draining the mammary gland of the dog. The tissues at the site of local injection tolerated large amounts of the isotope and general body distribution was well below a dangerous level for the animal. The major problem in previous experiments was that often there was not homogeneous distribution of the particles within the lymph node, hence irradiation effects were patchy and often large areas of the nodes remained undamaged. This difficulty was also encountered when $Au^{198}$ was similarly studied(6).

It seemed to us that the amount of rare-earth carrier might influence homogeneity of particle distribution and therefore distribution of irradiation effect. Two factors might be expected to play a role in such a study. The first is that high carrier doses (low specific activity) of radioactive rare-earths tend to remain at site of injection, whereas low carrier or carrier-free doses (high specific activity) show a greater tendency to be mobilized away from site of injection(3). If we desire to damage the regional lymph nodes of a given area, and to prevent local irradiation damage at site of injection, the material with high specific activity would seem to be advantageous. The other problem concerns the total mass of rare-earth particles available to saturate a lymph node. In previous studies we had injected up to 131 mc of $Lu^{177}$ into the mammary gland of a dog without producing consistent homogeneous radiation effect. In any given node considerably more total concentration of radioactivity was present than was necessary to produce the desired effect; on the other hand, the nodes contained "cold" spots. Dilution of the radioactive particles by additional nonradioactive material would therefore be a possible approach to even dispersion in lymph nodes and their more nearly complete destruction with much lower curiage. This study was undertaken to determine the over-all effect of the specific activity of $Lu^{177}$ on its intranodal pattern. A mixed carrier of stable lutecium and stable yttrium was used in the preparations of low specific activity. The heterogeneous

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carrier was based on previous study of this and of other combinations of rare-earth elements as carrier for the same radioisotope (4).

*Method.* Two groups of female dogs were used. From 22 mc to 35 mc of $Lu^{177}$ was injected into the right superior mammary gland of each animal. Two weeks later the animals were autopsied. Specimens from site of injection, regional lymph nodes, distant lymph nodes, marrow, liver, spleen, lungs, kidneys, heart, and other selected organs were obtained. Counts for radioactivity were made from a portion of each specimen by means of a wet-ashing method and end-window Geiger-Muller tube. Lymph nodes and other selected organs were examined histologically and autoradiograms were made.

Group A consisted of 5 dogs that received lutecium 177 in preparations of low specific activity. The high level of carrier contained both lutecium and yttrium and specific activity was expressed as millicuries of the radioisotope per mg of total carrier. An average preparation of this type was produced by activation of 30 mg of lutecium oxide (99.9%) in the graphite reactor at Oak Ridge and processing the activated oxide according to the radiochemical procedure described previously(1). The yield was ordinarily from 100 to 120 millicuries of radiolutecium in 10 ml of an isotonic solution of lutecium chloride and sodium chloride at pH 3.5 to 4.0. The dose for one dog was prepared by mixing a portion of the radioassayed solution with a slightly acid standard solution of yttrium chloride (pH 4.0, 60 mg of yttrium per ml) and diluting so that 10 ml contained 30 to 35 millicuries of radiolutecium and 150 mg of yttrium. The combined concentration of lutecium and yttrium was approximately 0.16 molar of which 8% was due to lutecium. The specific activity of 3.3 mc of $Lu^{177}$ per mg of stable lutecium was reduced roughly to 0.25 mc per mg of total carrier by addition of yttrium.

Group B consisted of 12 dogs that received radiolutecium in preparations of high specific activity. The procedure for production of these preparations was designed to include a minimum amount of carrier. The oxide of high purity was first converted to a standard solution of lutecium nitrate in dilute nitric acid. An aliquot of this solution containing 2.0 mg of lutecium was placed in a small quartz ampoule, evaporated slowly to dryness in an oven at 100°C, and sealed *in vacuo*. The nitrate was activated for 3 weeks in the highest available flux ($1.5 \times 10^{13}$ neutrons $cm^{-2}$ $sec^{-1}$) of the low intensity testing reactor (LITR) at Oak Ridge. The activated nitrate was repeatedly extracted with 0.3 ml portions of 1.0 M hydrochloric acid until 98 to 99% of the radioactivity was obtained in 1.2 to 1.5 ml of the acid. The acidic solution was partially neutralized and adjusted in volume to give an isotonic solution at pH 3.5 to 4.0. The yield of radioisotope was ordinarily $100 \pm 25$ millicuries per mg of stable lutecium. The final concentration of lutecium was approximately $5 \times 10^{-4}$ molar and the specific activity was roughly 300 times that of the preparations of low specific activity.

*Results.* When a previous experiment consisting of 8 dogs receiving from 24 to 131 mc of $Lu^{177}$ was used as a base line for comparison, the results in Group A left much to be desired. The site of injection did not tolerate the high-carrier material and severe reactions were the rule. Three of the 5 animals developed large ulcers at site of injection. The other 2 showed evidence of severe acute radiation damage to the skin, subcutaneous tissue, and muscle. Obviously a large amount of radioactivity remained at site of injection. This was further reflected in the axillary, latissimus dorsi, and intercostal lymph nodes. These are the nodes that drain the superior mammary gland, and those that one would expect to accumulate the bulk of the isotope. This had been true in previous experiments with $Lu^{177}$(1) and $Au^{198}$(5). Whereas counts for radioactivity were comparatively high in the regional lymph nodes, concentration of the isotope and radiation effect was spotty. The isotope tended to form a sludge in the afferent lymphatic spaces and only rarely showed diffuse concentration in a given lymph node. The sludge could readily be seen in histological sections stained with H. and E. The particulate matter was surrounded by extensive foreign body reaction; for the most part the rest of the node remained undamaged. (Fig.

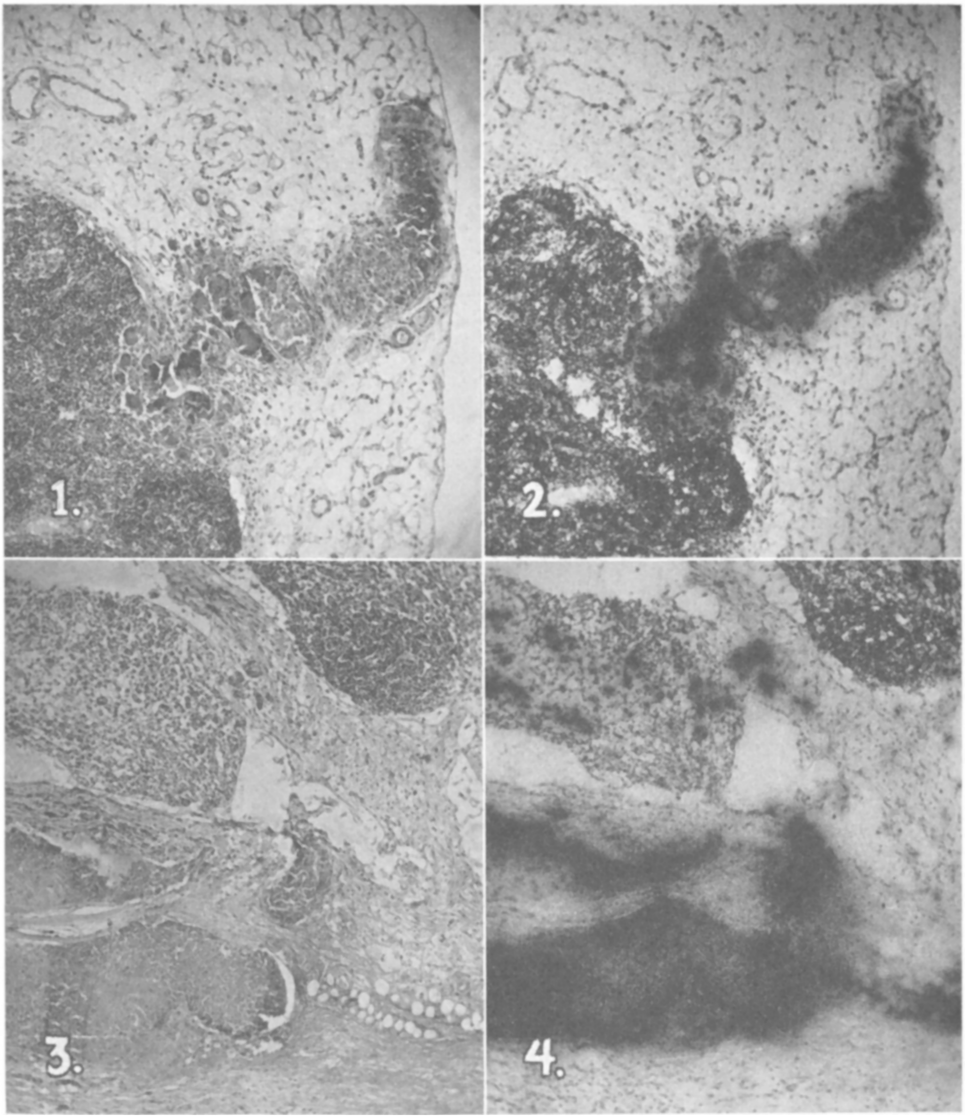


FIG. 1. Right axillary lymph node obtained 2 wk after inj. of 22 mc $Lu^{177}$ into right superior mammary gland. The isotope has formed a sludge in peripheral sinus and perinodal lymphatic vessel.

FIG. 2. Autoradiogram of node illustrated in Fig. 1. Radioactivity limited to the sludge.

FIG. 3. Right latissimus dorsi lymph node showing sludge of isotope in perinodal fat.

FIG. 4. Autoradiogram of node shown in Fig. 3. Note distribution in lymphoid tissue, with high conc. in vascular space.

1 and 3). Autoradiograms showed that intense radioactivity was limited to the areas of sludge (Fig. 2 and 4). A rare node showed good distribution of radioactivity; however, in no instance were all the draining nodes effectively irradiated. No appreciable activity was present in the other organs of the body.

The radiation effect in the regional lymph nodes of the 12 dogs in Group B was very much better than that obtained in Group A animals. None of the dogs showed severe reaction at the injection site. Slight edema and acute inflammation were present, but no appreciable radiation necrosis was found. Radioactivity counts were high in the lymph nodes draining the site of injection and there

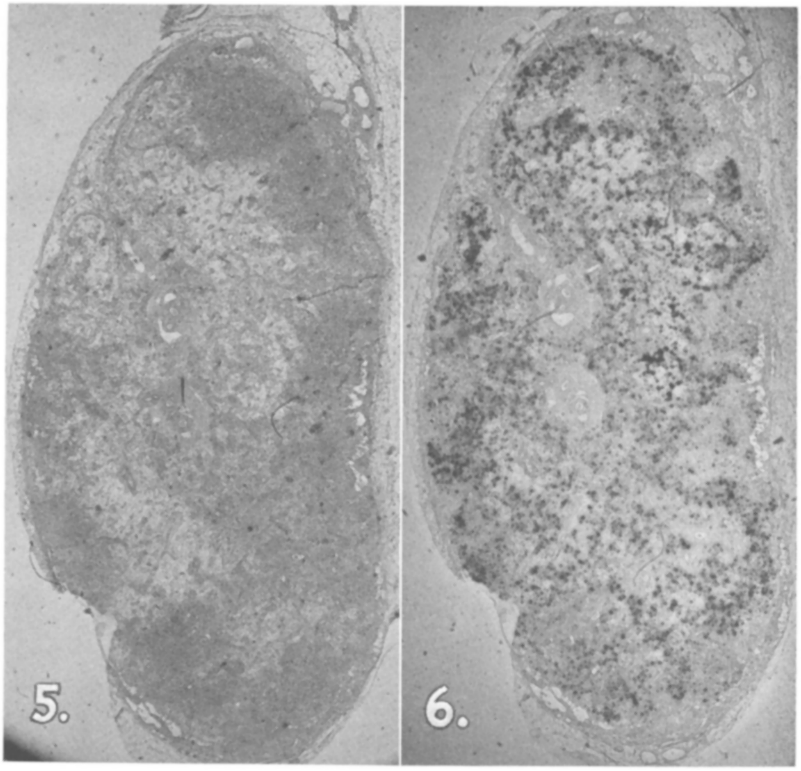

FIG. 5. Right axillary lymph node after inj. of low carrier (high specific activity 2) $Lu^{177}$. Destruction of node is complete.
FIG. 6. Autoradiogram of lymph node in Fig. 5. Uniform distribution of activity.

was no appreciable general body distribution in such organs as the bone marrow, spleen, or liver. Histological sections and autoradiograms of the organs showed radioactivity and radiation damage limited to the right latissimus dorsi, right axillary, and intercostal lymph nodes. On occasions there was slight activity in the right cervical nodes, but never any radiation necrosis. The lymph nodes on the left side of the body served as controls and showed neither activity in the autoradiograms nor radiation changes. In 3 of the 12 dogs the regional lymph nodes were destroyed. (Fig. 5 and 6). Seven other animals showed partial destruction of some of the nodes with spotty distribution in others. (Fig. 7). In two animals the concentration of the isotope and intranodal distribution was no better than in the Group A animals.

*Discussion.* The avidity of lymph nodes for radioactive colloids has led to the investigation of their potentialities for selectively irradiating a set of regional lymph nodes in the dog. The colloidal behavior of rare earths at body pH, and the radiation characteristics of $Lu^{177}$ in particular, make it a theoretically useful agent. The great obstacle, however, seems to be the nonhomogeneous distribution of particles within a given set of nodes, even when large amounts of the isotope are used. Since $Lu^{177}$ is chiefly a beta-particle emitter with relatively few low-energy gamma radiations per disintegration, homogeneity of particles must be obtained before one can hope for generalized nodal distribution. When particles of radioactive lutecium are closely packed, more than enough radiations are emitted to destroy the tissue. Greater dispersion of particles was not obtained by mixing with a large chemical dose of nonradioactive particles. The additional inactive rare earth tends to form a sludge blocking the afferent lymphatics thus preventing the isotope from circulating through the lymph node.

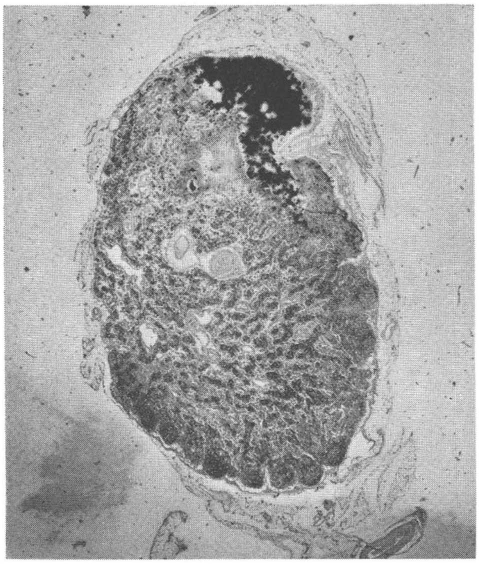

FIG. 7. Focal concentration of radioactivity in lymph node.

Perhaps chemical toxicity plays a part in this phenomenon. It would also seem possible that the radiations play a role in sealing off the afferent lymphatics thus preventing general distribution of the isotope throughout the node.

On the other hand, carrier-free $Lu^{177}$ (high specific activity) is more readily mobilized from the site of injection and incarcerated in the regional lymph nodes. Its distribution within the lymph nodes is much more homogeneous and its resultant radiation effects are more generalized. Intranodal distribution, however, is often uneven and therefore irradiation is inadequate. Certainly the specific activity of the isotope plays a role, then, in the ultimate pattern of distribution; but unless other presently unknown factors can be controlled the problem of homogeneous intranodal distribution remains unsolved. The compound in these studies was lutecium chloride. Preliminary work indicates that certain lutecium complexes might be more effective.

*Summary.* When $Lu^{177}$ is injected into the mammary gland of the dog it travels via the lymphatics to the regional lymph nodes. It is concentrated in the lymph nodes and irradiates them. No appreciable amount of radioactivity is accumulated in other organs. A study of the influence of the specific activity of $Lu^{177}$ on its intranodal distribution indicates that a much more effective pattern can be obtained with carrier-free $Lu^{177}$. High-carrier doses on the other hand produce severe radiation damage at site of injection and ineffective amounts are concentrated within the lymph nodes.

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