Time and Site Study for Optimum Lymph Node Concentration of Radiogold Following Intrabronchial Injection

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Radioactive colloidal gold has been said to be unsatisfactory for therapeutic use in delivering radiation to the regional lymph nodes of the lung following intrabronchial instillation. The objection to the use of this method was that the gold drained very slowly to the lymph nodes, requiring from 10 days to 2 weeks, and did not concentrate within the range of its effectiveness (3). Silver-coated radiogold was found to reach the lymph nodes in significant amounts after 5 days (4). Recent work has demonstrated that, when radioactive colloidal gold is injected into the submucosa of the bronchus, the colloidal sol is transported via the lymphatics from the site of injection to the regional lymph nodes where it is trapped and concentrated (1). If instillation were combined with intrabronchial injection, the combination might prove of therapeutic use in radiating both the primary tumor and regional lymph nodes in inoperable bronchiogenic carcinoma (5). Since the half-life of Au198 is only 2.7 days, the time required for concentration of the gold within the lymph nodes following intrabronchial injection becomes a decisive factor in determining whether or not effective radiation could be obtained.

In previous experiments the intermediate bronchus was utilized (1, 2). This site was chosen because it was easily identified, easily approached, and was the lowest accessible site in the dog. This study was undertaken to determine the time required for effective lymph node concentration and the optimum site or sites of injection.

MATERIALS AND METHODS

Radioactive colloidal Au198, with particle sizes ranging from 0.003 to 0.004 μ, was used.1 The isotope has a half-life of 2.7 days and possesses suitable radiation characteristics (5). It emits beta rays with maximum energy of 0.97 Mev and gamma rays of 0.411 Mev. Fifty per cent of the beta rays penetrate only 0.88 mm. and are the primary source of the radiation effect in localized areas. The gamma rays penetrate deeply and are useful in external counting but may also contribute to both local and total-body radiation.

In all experiments 2–3 mc. of Au198, diluted 1 mc. to 1 cc. of normal saline solution, was injected under direct vision through a long needle into the submucosa of the tracheobronchial tree (Chart 1, Site T1). In the study on the time required for concentration, the Au198 was injected into the submucosa of the intermediate bronchus of fourteen mongrel dogs. The dogs were autopsied at intervals ranging from 1 to 72 hours. Specimens were weighed and measured for radioactivity by the wet ash method with the use of an end-window Geiger-Müller tube. All figures are recorded as counts/min/gm of fresh tissue corrected for decay from the time of animal injection. Histological sections and autoradiographs were prepared on selected specimens. Fifteen dogs were given injections of similar doses and sacrificed at intervals ranging from 1 to 5 weeks. The histological changes in these nodes were compared with those of the

1 Abbott Laboratories, Oak Ridge, Tenn.
CHART 1.—Schematic diagram of lung and regional lymph nodes of dog indicating areas of assay.

CHART 2.—Schematic diagram of hilar lymph nodes indicating concentration of activity within 72 hours. The number next to each lymph node represents 1,000 counts/min.
short-term dogs. In addition to the lymph nodes, counts were routinely made on each lobe of the lung, heart, liver, spleen, omentum, and kidney.

For the experiments on the optimum site of injection at the Au$^{198}$, nine separate injection sites were chosen (Chart 2). The lowest site, T1, is the intermediate bronchus and was the site used in previous experiments. The other eight sites are located at 1-inch intervals on either side of the trachea. Two animals were given injections at each site, with the exception of T9, where one animal was used. The dogs were autopsied from 5 to 14 days following injection. The regional lymph nodes and viscera were measured for radioactivity. Autoradiographs and histological sections were made on the lymph nodes and selected tissues.

**RESULTS**

*Time required for concentration.*—The results of these experiments demonstrate little lymph node concentration in the 1- and 2-hour injections, but by 4 hours high levels of activity were demonstrated in the hilar lymph nodes. These high level concentrations persisted in all animals through 72 hours, although there was considerable variation in individual node concentrations from dog to dog (Chart 3). This latter variation might be explained in part by the facts that one-half of the node was used for tissue study and that the assays were not representative of the entire structure. It is apparent from the autoradiographs in this and other studies that the concentration within the lymph nodes is of patchy nature. Counts on the other viscera were characteristically low, usually below 100 counts/min/gm of tissue.

These experiments thus show that colloidal radiogold of this particle size readily reaches the hilar lymph nodes within the effective activity range of the isotope. It is further demonstrated that the radioactivity is well localized to this

![Chart 3](chart3.png)

*Chart 3.*—Schematic diagram of tracheobronchial tree of dog indicating sites of injections and relative concentration of activity in the hilar lymph nodes. The number next to each lymph node represents 1,000 counts/min.
single area of lymph drainage and is not distributed in any appreciable amount to other organs.

Autoradiographs at 1 hour showed very little darkening of the emulsion. At $\frac{3}{4}$ hours there was marked activity which persisted throughout the 72-hour animals (Fig. 1). Prior to 1 day there were no lymph node changes which could be definitely attributed to radiation; however, small particles of black pigment resembling gold were present in the macrophages of the lymph nodes. At 24 hours definite pyknosis of the lymphocytes was discernible. There was an apparent decrease in lymphocytes as well as an increase in pigment-containing macrophages (Figs. 2 and 3). Sections from the long-term animals showed definite and often extensive necrosis and vascular thrombosis within the lymph nodes (Fig. 4). This change was present within 1 week and was seen in all animals throughout the 5 weeks. The necrosis varied from focal to confluent areas involving a major portion, but never the entire node. After 1 week there was always a depletion of lymphocytes and a marked increase in reticular cells. Heavy deposits of black pigment were found in and about the necrotic areas. Again it should be stressed that the dispersion of the sol within the lymph node and the histological changes were rarely of a diffuse nature. Routine sections of liver, spleen, bone marrow, kidney, and local injection site showed no significant changes.

The colloid used in these experiments has a lower specific activity than the gold irradiated in the Brookhaven National Laboratory pile. It has been shown that the lymph nodes concentrate at least twice as much activity in the case of the higher specific-activity gold (6).

Optimum Site of Injection.—The relative activity of the individual lymph nodes is illustrated in Chart 2. The greatest concentration of activity in the greatest number of lymph nodes resulted from injection into the most dependent sites, T1, T2, and T6. Lower concentrations and fewer active nodes were encountered as the injection site proceeded up the trachea. Injections over 1 inch above the carina were relatively ineffectual in concentrating radioactivity in the parabronchial and subcarinal lymph nodes. In the lower tracheobronchial tree concentration was always higher in the ipsilateral lymph nodes. Histologic changes in the lymph nodes reflected the amount of radioactivity in the individual node. Necrosis was present only in those nodes where high concentrations of radioactivity existed. This pattern of distribution suggests that multiple sites of injection low in the tracheobronchial tree would afford a maximum concentration of radioactivity in the parabronchial and subcarinal lymph nodes.

SUMMARY
1. Colloidal $^{198}$Au was injected into the bronchial mucosa of dogs in an attempt to determine the rapidity of concentration within the regional lymph nodes and the site of injection for optimum concentration within the nodes.

Specimens of the regional lymph nodes and viscera were measured for radioactivity. Histologic sections and autoradiographs were examined and compared with those from a group of animals receiving a similar dosage of $^{198}$Au and sacrificed in from 1 to 5 weeks.

2. Colloidal radiogold of this particle size concentrated within the regional lymph nodes well within the effective activity range of the isotope. Radioactivity was concentrated in the lymph nodes and was not distributed in any appreciable amount to other organs.

3. The most effective site of injection within the bronchial tree was found to be the most dependent accessible site within the bronchus.

4. Radiation necrosis within the lymph nodes had a patchy distribution when small doses of $^{198}$Au were used. This distribution was confirmed by autoradiographs.

REFERENCES

Fig. 1.—Dog 212. Right subcarinal lymph node radio-autograph showing concentration of activity at $\frac{3}{4}$ hours after injection.

Fig. 2.—Dog 104. Left paratracheal lymph node. H. & E. section showing phagocyossed $^{198}$Au and lysis of lymphocytes.

Fig. 3.—Dog 104. Left paratracheal lymph node. Radio-autograph showing concentration of activity 72 hours after injection.

Fig. 4.—Dog 122. Right subcarinal lymph node. H. & E. section showing necrosis 14 days after injection.
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