# Differential Uptake of Gallium-67-Labeled Liposomes Between Tumors and Inflammatory Lesions in Rats

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The differential gallium-67 ($^{67}$Ga) accumulation in tumors and inflammatory lesions in rats after i.v. injection of liposome encapsulated $^{67}$Ga ([$^{67}$Ga]liposomes) was studied. The $^{67}$Ga accumulation in the tumor was much greater than that in the granulation tissue regardless of the surface charge of liposomes; however, the difference between the two tissues was the greatest when using positive charged liposomes. Gallium-67 delivery to tumors by liposomes was greater than that to granulation tissue in all stages of growth. After i.v. injection, the accumulation of $^{67}$Ga in the tumor reached a maximum at 12 hr, whereas in the granulation tissue it was delayed to 24 hr postinjection. In the study of tissue distribution of $^{67}$Ga in rats bearing both tumor and granulation tissue, positively charged liposomes preferentially delivered $^{67}$Ga to the tumor than to the granulation tissue. These results suggest that [$^{67}$Ga] liposomes are able to discriminate between the tumor and the inflammatory lesion.

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The unique characteristics of liposomes as a microcapsule are being studied with keen interest and many investigations on the applications of liposomes in medicine and pharmacy are currently underway (*1–3*). The applications are expanded to various subjects such as controlled release of drugs, reduction of toxicity, protection of a drug from metabolism and immune response, and direction to a target location. In particular, the tumor accumulation of liposomes has been vigorously investigated for the purpose of using liposome for cancer chemotherapy (*3–5*) and cancer diagnosis (*6*). We also reported the excellent tumor uptake and tumor-to-blood ratio of gallium-67 ($^{67}$Ga) using liposome encapsulated $^{67}$Ga ([$^{67}$Ga]liposomes) that was prepared from distearoylphosphatidylcholine and cholesterol (*7*).

One of the major problems in the imaging of tumors using radiopharmaceuticals is their accumulation in the inflammatory lesion resulting in ambiguous diagnoses. The tumor imaging agents that are used clinically now, such as [$^{67}$Ga]citrate, accumulate not only in the tumor site but also in the inflammatory lesions. This makes it difficult to discriminate between the two by nuclear imaging techniques alone, and tumor-specific imaging agents are waiting to be developed. In this paper, we have studied the differences of $^{67}$Ga accumulation between a tumor and an inflammatory lesion after intravenous injection of [$^{67}$Ga]liposomes and discuss the possibility of using liposomes as a tumor-specific imaging agent.

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## MATERIALS AND METHODS

### Animals and Materials

Male rats of Donryu strain (80–100 g) were supplied commercially* and fed a standard pellet diet and water *ad libitum*.

Materials used in this work were as follows: L-α-distearoylphosphatidylcholine (DSPC), cholesterol (CH), stearylamine (SA) and dicetylphosphate (DCP);† oxine‡; nitrilotriacetic acid trisodium salt (NTA)§; carrageenin Seakem No. 202¶; [methyl-$^3$H] thymidine (359 mCi/mg)**. Carrier-free [$^{67}$Ga]citrate and carrier-free $^{67}GaCl_3$ were also used††.

### Preparation of Liposomes

Neutral liposomes were prepared from DSPC and CH (molar ratio 2:1); positive liposomes from DSPC,

CH and SA (10:5:1); negative liposomes from DSPC, CH and DCP (10:5:1) (*7*). Chloroform solutions of lipid mixtures were evaporated to dryness under a stream of nitrogen at 60°C. The dried films of lipid were then kept at reduced pressure overnight. To the lipid films were added 150 m*M* NaCl and 5 m*M* sodium phosphate (pH 7.4) (PBS) containing 1 m*M* NTA; lipids were suspended by vortexing. The suspension was sonicated in a Branson Sonifier (model 200) with a titanium microtip. Sonication was carried out at 20 kHz, a power level of 30 W for 30 min (continuous) at 60°C. After then, it was centrifugated at 20,000 *g* for 20 min to remove titanium fragments and any large liposomes. Untrapped materials in liposomes were removed by passage of liposomes through a Sephadex G-50 column (1 × 30 cm) in PBS. After gel filtration, liposomes were loaded with $^{67}$Ga by a modification of the method of Hwang et al. (*8*). Loading solutions containing 10 μl 0.55 m*M* oxine in ethanol, 100 μl 300 m*M* NaCl/20 m*M* sodium acetate (pH 5.5), and $^{67}GaCl_3$ in 0.1 N HCl with the desired activity diluted with deionized water to 100 μl prepared immediately before the loading process. This loading solution was added dropwise to 2 ml of the liposome suspension. The mixture was incubated at 37°C for 1 hr, then passed through the Sephadex G-50 column to remove nonloaded $^{67}$Ga. Electron microscopy after stain with potassium phosphotungstate showed the average diameter of the liposomes prepared as above to be ~60 nm (*7*).

### Transplantation of Yoshida Sarcoma

Yoshida Sarcoma (YS) ascites cells were used. Male Donryu rats, weighing 130–150 g, were subcutaneously injected in the left hind leg with 2 × $10^6$ cells.

### Carrageenin-Induced Inflammatory Tissue

Granulation tissue was induced by the modification of Selye's method using carrageenin as a phlogistic agent (*9*). Six milliliters of air was injected s.c. on the dorsum of rats (weighing 100–120 g) to make an air-pouch. After 24 hr, 4 ml of a 2% (w/v) solution of carrageenin in 150 m*M* NaCl was injected into the air pouch. The carrageenin solution was sterilized by autoclaving at 120°C for 15 min, and injected cooling 40–50°C. Immediately before the injection, penicillin and streptomycin were added to the carrageenin solution (0.1 mg each per ml of the solution).

### Tissue Distribution of $^{67}$Ga Radioactivity After Intravenous Injection of [$^{67}$Ga]Liposomes or [$^{67}$Ga] Citrate

Gallium-67 liposomes (1 mg as lipid and 1.5–2.5 μCi/0.3 ml/rat) or [$^{67}$Ga]citrate (2 μCi, 0.3 ml/rat) were injected into the tail vein of the rats that were bearing YS and/or produced carrageenin-induced inflammatory lesions. Rats weighing 150–170 g at the time of the injection of [$^{67}$Ga]liposomes were used except those rats used in the experiments on $^{67}$Ga uptake during the growth of the tumor and the granulation tissue. Rats were killed at various time intervals and the tissues were removed, weighed, and their radioactivities were counted with a gamma counter (Aloka ARC-300). At least four animals were used for each data point. Total injected dose was determined by assay of an aliquot of the administered liposome solution at the same time samples were assayed, using the same counter.

### Determination of [$^3$H]Thymidine Incorporation into DNA in Tumor and Granulation Tissue

Each rat received i.p. 20 μCi of [$^3$H]thymidine ($^3$H-TdR) 2 hr before killing. The tumor and the granulation tissue were removed, weighed, minced, and homogenized in 5 volumes of cold 30 m*M* Tris-HCl buffer (pH 7.4). Two milliliter aliquots of homogenate were each extracted with 2.5 ml of 10% trichloroacetic acid (TCA). The subsequent isolation of DNA was carried out according to the methods of Schmidt and Thannhauser (*10*) and of Schneider (*11*). Radioactivity in DNA fractions was measured in toluene-Triton X-100 (2:1) scintillator by using a liquid scintillation counter (Aloka LSC-900) after the removal of TCA by washing three times with 2 volumes of ether. The results were reported as dpm/g of tissue.

### Determination of Collagen Content in Granulation Tissue

Collagen content in the granulation tissue was determined by measuring hydroxyproline (OH-Pro) levels as described by Woessner (*12*). Aliquots of granulation tissue were hydrolyzed in 5 volumes of 6 N HCl in sealed tubes for 16 hr at 110°C in an oven. The hydrolysate was titrated to pH 7.0 with NaOH and diluted with deionized water. The diluted hydrolysate was filtered and 1-ml aliquots were assayed for OH-Pro content.

## RESULTS

Table 1 shows the biodistribution of $^{67}$Ga in rats bearing YS tumor or granulation tissue induced by carrageenin at 24 hr after administration of [$^{67}$Ga] liposomes. Three types of liposomes (positive, negative, and neutral) were studied. Each liposome was injected intravenously into the rats that were transplanted YS 3 days earlier or were injected s.c. carrageenin 6 days earlier. It was found that $^{67}$Ga accumulation in the tumor was significantly higher than that in the granulation tissue when any types of liposomes were injected (Student's t-test at $p < 0.001$ with positive and neutral liposomes and at $p < 0.01$ with negative liposomes). Tumor to muscle ratio and tumor to blood ratio was also much higher than granulation tissue to muscle ratio and granulation tissue to blood ratio, respectively.

**TABLE 1**
Biodistribution of $^{67}$Ga in Rats Bearing Yoshida Sarcoma or Granulation Tissue Induced by Carrageenin at 24 hr After i.v. Injection of [$^{67}$Ga]Liposomes

| Organ | Gallium-67 uptake (% administered dose/g of tissue)* | | | | | |
|---|---|---|---|---|---|---|
| | Tumor-bearing rats | | | Granulation tissue-bearing rats | | |
| | Positive | Negative | Neutral | Positive | Negative | Neutral† |
| Tumor | 6.23 ± 0.70 | 2.67 ± 0.23 | 6.89 ± 0.62 | — | — | — |
| Granulation tissue | — | — | — | 1.16 ± 0.17 | 1.56 ± 0.30 | 1.92 ± 0.20 |
| Liver | 2.82 ± 0.41 | 3.25 ± 0.17 | 3.50 ± 0.57 | 4.58 ± 0.60 | 3.14 ± 0.57 | 2.89 ± 0.32 |
| Spleen | 9.30 ± 0.54 | 10.28 ± 1.92 | 8.39 ± 0.92 | 3.54 ± 0.36 | 8.24 ± 0.77 | 9.18 ± 0.98 |
| Kidney | 0.85 ± 0.13 | 1.02 ± 0.06 | 0.90 ± 0.09 | 0.76 ± 0.08 | 0.85 ± 0.06 | 0.67 ± 0.10 |
| Lung | 0.81 ± 0.02 | 0.48 ± 0.06 | 0.79 ± 0.08 | 0.42 ± 0.11 | 0.35 ± 0.04 | 0.42 ± 0.10 |
| Heart | 0.67 ± 0.09 | 0.39 ± 0.05 | 0.72 ± 0.04 | 0.35 ± 0.09 | 0.40 ± 0.03 | 0.81 ± 0.15 |
| Muscle | 0.16 ± 0.01 | 0.09 ± 0.04 | 0.10 ± 0.02 | 0.09 ± 0.01 | 0.09 ± 0.02 | 0.06 ± 0.02 |
| Blood | 1.01 ± 0.11 | 0.21 ± 0.03 | 0.93 ± 0.09 | 0.60 ± 0.10 | 0.56 ± 0.10 | 1.23 ± 0.30 |
| T/M‡ | 38.94 ± 5.01 | 29.66 ± 13.43 | 68.90 ± 15.11 | — | — | — |
| T/B§ | 6.17 ± 0.97 | 12.71 ± 2.12 | 7.41 ± 0.98 | — | — | — |
| G/M¶ | — | — | — | 12.89 ± 2.34 | 17.33 ± 5.09 | 32.00 ± 11.17 |
| G/B** | — | — | — | 1.93 ± 0.28 | 2.78 ± 0.73 | 1.56 ± 0.41 |

* Mean values ± s.d.
† Charges of liposome surface.
‡ Tumor to muscle ratio.
§ Tumor to blood ratio.
¶ Granulation tissue to muscle ratio.
** Granulation tissue to blood ratio.

Positive and neutral liposomes provided the marked delivery of $^{67}$Ga to the tumor tissue, and positive liposomes showed the least delivery to the granulation tissue. Thus, positive liposomes appeared to be the most advantageous to discriminate between the tumor and the inflammatory lesion.

Figures 1 and 2 show the changes of $^{67}$Ga uptake, following the administration of $^{67}$Ga-positive liposomes ($^{67}$Ga-(+)liposomes), in the tumor and the granulation tissue during their growth. Gallium-67-(+)liposomes was injected intravenously into the rats 24 hr before killing. After the transplantation of YS cells, the tumor weight increased steeply until Day 6 followed by a slower increase. DNA synthesis, indicated by the incorporation of $^{3}$H-TdR, was activated between Day 3 and Day 6. The total uptake of $^{67}$Ga in the tumor increased

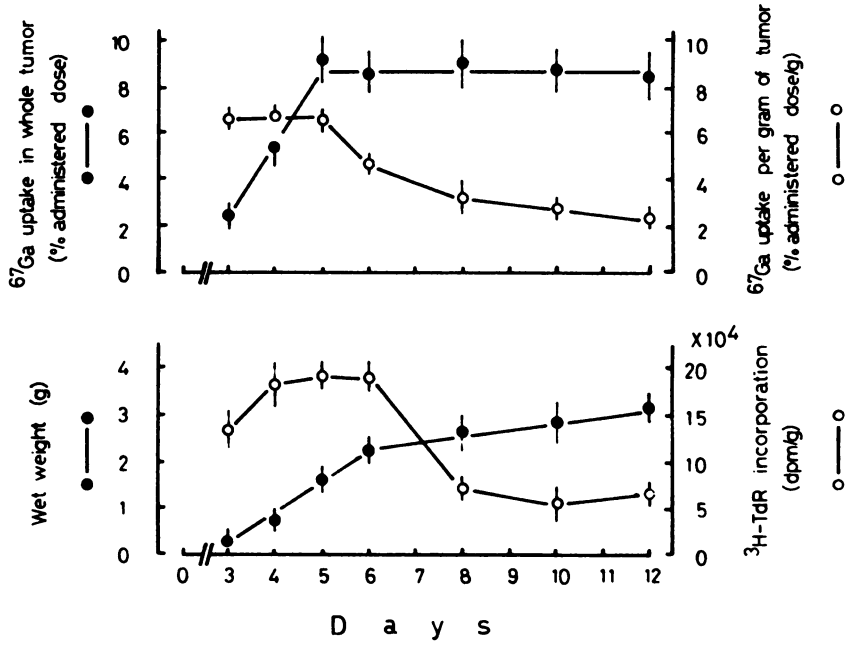


**FIGURE 1**
Changes of $^{67}$Ga uptake by tumor during tumor growth postadministration of $^{67}$Ga-(+)liposomes. Each point in this and subsequent Figs. 2, 3, and 4 represents mean ± s.d.

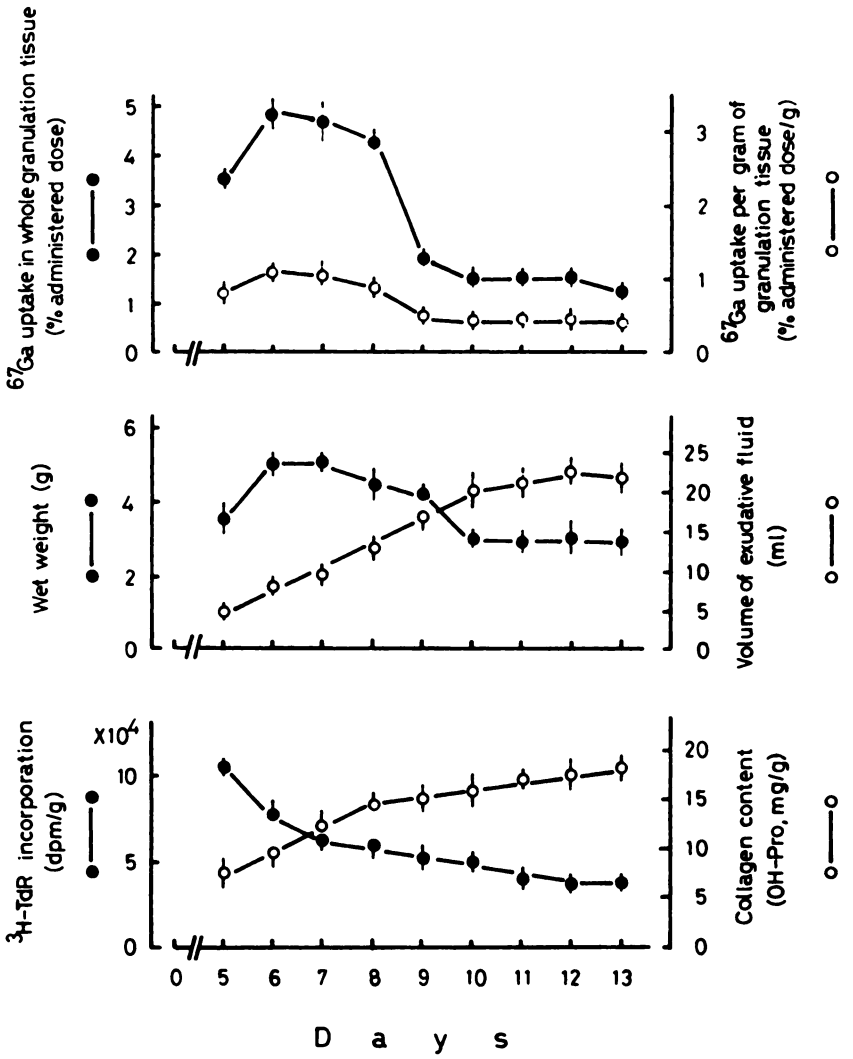


**FIGURE 2**
Changes of $^{67}$Ga uptake by granulation tissue during its growth postadministration of $^{67}$Ga-(+)liposomes

in proportion to the weight increase until Day 5, where it reached about 9% of the administered dose, and then kept constant at this level. Gallium-67 uptake per gram of tumor was almost constant till Day 5 (about 6.5% administered dose per gram of tissue) and then decreased. By Day 14 all of the animals had died. In the development of carrageenin-induced inflammatory, a capsule of newly formed granulation tissue arose within a few days after carrageenin injection from the subcutaneous tissue surrounding the carrageenin layer and could be separated from the surrounding tissue after Day 5. Wet weight of granulation tissue reached a maximum at Days 6 and 7, and then decreased slowly. The volume of the exudative fluid in the pouches continued to increase till Day 10 and remained nearly constant. $^{3}$H-TdR incorporation was already decreasing by Day 5. Collagen content continued to increase during the experimental period. During either tumor growth or development of granulation tissue, the variation of $^{67}$Ga uptake in other tissues after the administration of $^{67}$Ga-(+)liposomes was scarcely observed.

Figures 3 and 4 show the time course of $^{67}$Ga uptake in the tumor and the granulation tissue after the administration of $^{67}$Ga-(+)liposomes were injected i.v. into the rats 3 days after tumor transplantation or 6 days after carrageenin injection. The $^{67}$Ga uptake in the tumor reached a maximum 12 hr after injection, remained at this level for 24 hr, and then decreased slowly. The maximum value was 6.2% administered dose per gram of tissue. On the other hand, the $^{67}$Ga uptake in the granulation tissue rose until 24 hr after injection and then become constant. The uptake value was 1% administered dose per g of tissue at its maximum.

As a further trial, the tissue distribution of $^{67}$Ga in rats that had both the tumor and the granulation tissue was examined after the administration of $^{67}$Ga-(+)liposomes (Fig. 5). Animals were injected s.c. with carrageenin followed by transplantation of YS after 3 days, and were injected i.v. with $^{67}$Ga-(+)liposomes after another 3 days. After 24 hr, they were killed and the tissue distribution of $^{67}$Ga radioactivity was followed. Gallium-67 citrate was administered in the same manner in order to make a comparison with the $^{67}$Ga-(+)liposomes. Figure 5 is expressed as the ratio of $^{67}$Ga-radio-

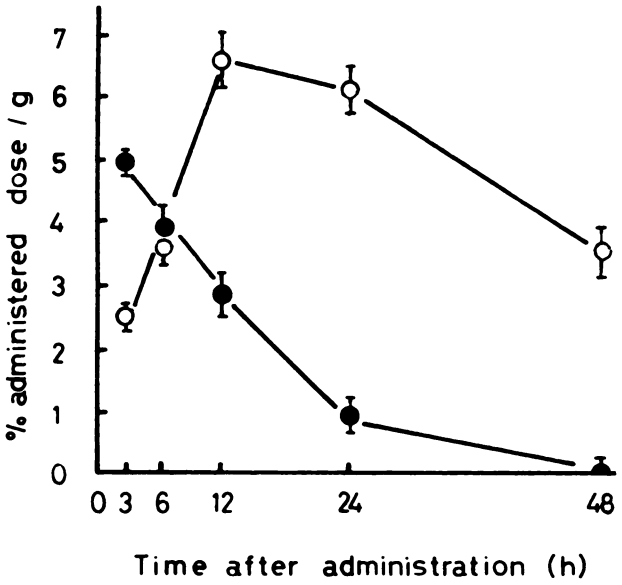


**FIGURE 3**
Uptake and retention of $^{67}Ga$ in tumor and blood of rats bearing YS postadministration of $^{67}Ga$-(+)liposomes. (○) Tumor; (●) Blood

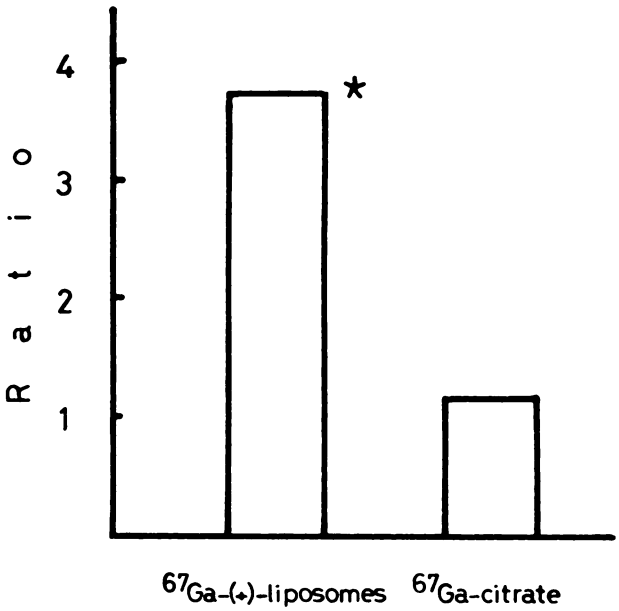


**FIGURE 5**
Tumor to granulation tissue ratio of $^{67}Ga$ radioactivity distribution at 24-hr postadministrations of $^{67}Ga$-(+)liposomes and [$^{67}Ga$]citrate. * = Significantly different at $p < 0.01$

activity accumulating in 1g of tumor to that in 1 g of granulation tissue. Owing to bearing both tumor and granulation tissue in the same animal, the tissue distribution of $^{67}Ga$ following the administration of $^{67}Ga$-(+)liposomes was a little different from that in the rats which were bearing tumor or granulation tissue separately (data not shown). However, it was obvious that $^{67}Ga$ uptake in the tumor was far greater than in granulation tissue when $^{67}Ga$ was delivered by the positive liposomes. The tumor to granulation tissue ratio of radioactivity from $^{67}Ga$-(+)liposomes was 3.8. In comparison, this ratio for [$^{67}Ga$]citrate was merely 1.2, indicating that [$^{67}Ga$]citrate accumulates about the same in the tumor as in the granulation tissue.

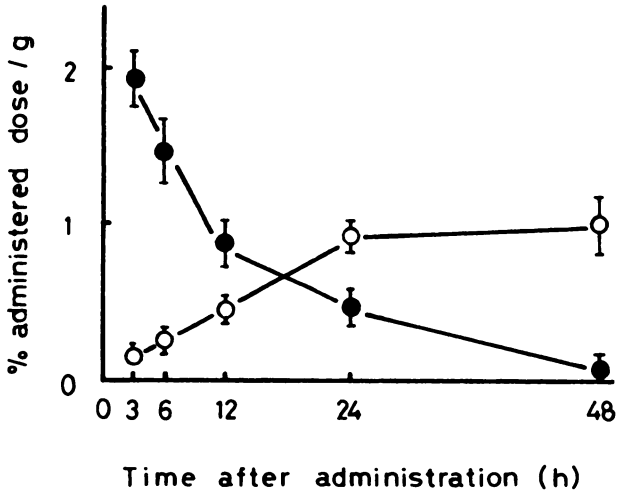


**FIGURE 4**
Uptake and retention of $^{67}Ga$ in granulation tissue and blood of rats bearing carrageenin-induced inflammation postadministration of $^{67}Ga$-(+)liposomes. (○) Granulation tissue; (●) Blood

## DISCUSSION

Several early works have found that liposomes had some selective affinity for various tumors (*7,13–15*). On the other hand, it is well known that liposomes are taken up by Kupffer cells in the liver and macrophages in the spleen that are associated with the reticuloendothelial system (RES). It is also expected that liposomes have some affinity for the inflammatory lesion, where polymorphonuclear leukocytes and macrophages assemble.

However, Morgan et al. (*16*) reported that positive and neutral liposomes accumulated little in inflammatory lesions, whereas negative liposomes did accumulate in the experimental Staphylococcal abscesses. Multilamellar vesicles (MLVs), which range in size from 0.1–1 $\mu$m in diameter, were taken up mostly by RES, while small unilamellar vesicles (SUVs), 0.03–0.08 $\mu$m, may partially avoid clearance by the RES (*13*). These observations suggest that the accumulation of liposomes in the inflammatory lesion is controlled by factors such as size and/or charge of the liposomes. We have attempted to find liposomes which can deliver radionuclides, such as $^{67}Ga$, indium-111, and technetium-99m, to the tumor tissues specifically by regulating such factors. As we have observed that the $^{67}Ga$ accumulation in the tumor after the injection of SUVs carrying $^{67}Ga$ is much

greater than that with MLVs (*7*), we began this study with the check of effects of surface charge of liposomes using SUVs.

As shown in Table 1, liposomes of any charge (positive, negative, or neutral) delivered larger amounts of $^{67}$Ga to the tumor than to the granulation tissue; however, quantitative difference of $^{67}$Ga accumulation between them using positive liposomes was the greatest of the three. It indicated that $^{67}$Ga-(+)liposomes are favorable for discriminating between the two lesions. The effects of surface charge of liposomes were reported on their stability in blood circulation (*17,18*), the tissue distribution in normal mice (*19*), the accumulation in tumor (*14,15*), in myocardial infarction (*20*), in lymph nodes (*21*), in inflammatory lesions (*16*), and immunopotentiation (*22*), etc. However, none of these studies gave clear explanations for such surface charge effects, though several hypotheses are presented. Juliano and Lin (*23*) found that liposomes with different surface charges bind different arrays of plasma proteins and suggested that bound proteins may play important roles in the fate of liposomes in vivo. In addition, it has been observed in in vitro studies that liposomes can interact with cells by various mechanisms, such as fusion, endocytosis, lipid exchange and stable adsorption, owing to surface charge and lipid composition of liposomes and properties of the cell surface (*24*). Therefore, specific interactions of a tissue with liposomes of a certain surface charge may also exist in vivo and it may result from a particular property of cell surfaces and cell environments.

In spite of the injection of the same $^{67}$Ga-(+)liposomes preparation, $^{67}$Ga uptake by the liver of rats bearing the granulation tissue was larger than that of the tumor-bearing rats (Student's t-test at $p < 0.05$), and $^{67}$Ga retention in the blood of the former was less than that of the latter (not significant) (Table 1). Figures 3 and 4 also show the $^{67}$Ga clearance in the blood of the former after i.v. injection of $^{67}$Ga-(+)liposomes was more rapid than that of the latter. Such differences were not observed as to negative and neutral liposomes (Table 1), and they could account for the low $^{67}$Ga accumulation in the granulation tissue using $^{67}$Ga-(+)liposomes. As such differences were found when the same $^{67}$Ga-(+)liposomes preparations were injected, it is presumed that they result not from the heterogeneity of liposome particle size but from some charge effect when using positive liposomes.

We observed the changes of $^{67}$Ga accumulation in the tumor and in the granulation tissue during their growth using $^{67}$Ga-(+)liposomes (Figs. 1 and 2). Until the fifth day after tumor transplantation, DNA synthesis was activated and the tumor weight increased steeply. During this period, $^{67}$Ga uptake per g of tumor was relatively high and constant (~6.5% administered dose). This value was one of the highest of all organs. The total $^{67}$Ga uptake by the tumor increased parallel to tumor weight, but after Day 5, the uptake per g of tumor began to decrease. This observation agrees with that of Proffitt et al. (*25*). It is presumed to result from the increase of necrotic areas, which may be inaccessible to circulating liposomes. The reason for the efficient delivery of $^{67}$Ga to the tumor by liposomes has not been elucidated yet, but our results suggest the rapid growth of tumor takes part in it. In the development of carrageenin-induced inflammation, $^{67}$Ga uptake in the granulation tissue was rather high in terms of total uptake and in terms of uptake per g of tissue during Day 5 and Day 8, but after then both of them decreased. Although the variation pattern of $^{67}$Ga uptake was similar to that of weight of the granulation tissue, we have no further information on the relation between them. As the weight of granulation tissue is an index of total inflammation, the more vigorous the inflammation is, the more liposomes may deliver $^{67}$Ga to the granulation tissue. But $^{67}$Ga in the granulation tissues delivered by $^{67}$Ga-(+)liposomes was 1% administered dose per g of tissue at the highest during this experiment period. This value is higher than that of the surrounding tissue; however, it was merely about one-fifth of that in the tumor. Therefore, it is expected that $^{67}$Ga-(+)liposomes deliver $^{67}$Ga to the inflammatory lesion much less than to the tumor at any stage of inflammation. Further study is needed to confirm this, using other models of tumor and inflammation.

Figures 3 and 4 show $^{67}$Ga delivery by $^{67}$Ga-(+)liposomes to the granulation tissues was not only less quantitatively, but also slower than that to the tumor. There are two assumptions that explain the delayed delivery of $^{67}$Ga by the liposomes to the granulation tissue. One is that phagocytic leukocytes in blood engulf the liposome (*26*) and then carry them to the granulation tissue. The other is low blood flow in the granulation tissues. Parnham et al. (*27*) have reported that the blood flow in the carrageenin-induced granulation tissue was lower than that in the normal tissues. Blood flow of the granulation tissue induced by open wounds was also low, though it was higher than that in the skin (*28*). It is known that tumor blood flow is generally low (*29,30*), but it is higher than that in the granulation tissues before the necrotic areas appear (*31*).

Although [$^{67}$Ga]liposomes used in the present study can deliver a good deal of $^{67}$Ga to the tumor tissues, clear explanations for this have not been made yet. The differences of the blood flow in the various tissues mentioned above cannot account for the efficient $^{67}$Ga delivery to the tumor, because the blood flow in the tumor is lower than that in normal tissues. It may correlate that construction and function of newly formed blood vessels at tumors are peculiar in comparison with normal vessels (*32*). Structural defects in the endothelium and basement membrane in the microcir-

culation were observed in a variety of tumors (*33*). New capillaries in the tumor leak fluorescein and colloidal carbon which normal capillaries do not (*32*). Hwang et al. (*34*) have reported that SUVs can leave the vascular space and slowly migrate to surrounding tissues. Therefore, it is possible that tumor vessels leak liposomes much more than normal ones because of their immaturity. The blood vessels in the granulation tissue are also newly formed and also have some gaps in the endothelial cells while they are immature (*35*). However, angiogenesis in certain nonmalignant processes, as granuloma formation, is turned off once the process is completed. By contrast, tumor angiogenesis is not self-limited and it continues indefinitely until all of the tumor is eradicated or until the host dies (*32*). The permanent immaturity of tumor blood vessels might allow liposomes to enter the tumor.

We would like to mention that the stability of liposomes is also a factor of the efficient delivery of radionuclides to the tumor. We have observed that the stable (low leakage of $^{67}$Ga) liposomes in the serum, which were prepared from DSPC/CH or sphingomyelin/CH, delivered a good deal of $^{67}$Ga to the tumor, while unstable ones did not (*36*). In addition, Williams et al. (*6*) have observed, using the perturbed angular correlation method, that the DSPC/CH liposomes remained intact in the blood over 24 hr or more. These observations suggested that the stability of liposomes in the blood circulation is important for the delivery of radionuclides to the tumor. Williams et al. also reported DSPC/CH liposomes were lysed rapidly in the EMT 6 tumor in contrast to their stability in the blood. This rapid lysis may contribute to the efficient $^{67}$Ga delivery by liposomes.

Finally, we studied the tissue distribution of $^{67}$Ga in rats that had both the tumor and the granulation tissue after the administration of $^{67}$Ga-(+)liposomes and [$^{67}$Ga]citrate (Fig. 5). Gallium-67 citrate shows much the same distribution as free [$^{67}$Ga]NTA in tumor-bearing animals (*7*). It became clear that $^{67}$Ga-(+)-liposomes delivered $^{67}$Ga to the tumor in preference to the granulation tissue, whereas there was little difference between them using [$^{67}$Ga]citrate. The accumulation of $^{67}$Ga in 1g of tumor was about fourfold higher than that in 1 g of granulation tissue. Since the delivery of $^{67}$Ga to the tumor by $^{67}$Ga-(+)liposomes was faster than that to the granulation tissue as shown in Figs. 3 and 4, it is possible to expand the difference further by setting the examined time earlier. This result suggests that [$^{67}$Ga] liposomes are able to discriminate between the tumor and the inflammatory lesion.

Further study is underway to elucidate the mechanisms which explain the differences between the delivery of $^{67}$Ga to the tumor and that to the inflammatory lesion by [$^{67}$Ga]liposomes.

## FOOTNOTES

* Nihon Rats, Urawa, Japan.
† Sigma Chemical Corp., St. Louis, MO.
‡ Wako Pure Chemical Industries, Ltd., Tokyo, Japan.
§ Nakarai Chemicals, Ltd., Kyoto, Japan.
¶ Marine Colloid Inc., Springfield, NJ.
** Amersham International, Buckinghamshire, England.
†† Nihon Mediphysics Co., Ltd., Takarazuka, Japan.

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