Studies of the In Vivo Uptake of Ga-67 by an Experimental Abscess: Concise Communication

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The blocking of Ga-67 plasma protein-binding sites—by administration of scandium citrate, ferric citrate, and a colloidal hydrous ferric oxide preparation—reduced the uptake of Ga-67 in normal soft tissues and also that in the viable portion of an experimental abscess. On the other hand, enhancement of Ga-67 plasma protein binding by administration of rabbit apotransferrin increased Ga-67 uptake in both abscess and normal soft tissues. These results indicate that the pathways of Ga-67 from blood into inflammatory processes and normal soft tissues may be similar. However, when Ga-67 plasma protein binding was increased by inducing anemia, a markedly decreased Ga-67 uptake in the abscess resulted, whereas uptake in normal soft tissue was still elevated. It is possible that the discrepancy between the effects of apotransferrin and anemia on abscess-tissue uptake of Ga-67 resulted from a secondary effect produced by anemia, i.e., a decrease in the macrophage population in the abscess. Taken as a whole, the results obtained suggest that Ga-67 leaves the blood and enters inflammatory lesions by pathways that are probably quite different from those in a soft-tissue tumor, and that the routes for abscesses may be similar to those occurring in normal soft tissues.

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We have recently presented evidence supporting our contention that different pathways are probably involved in the entry of Ga-67 into malignant and normal soft tissues (*1*,*2*). The fact that inflammatory processes also exhibit strong affinities for Ga-67 (*3*) raises a question as to whether the uptake of Ga-67 by such lesions occurs by a route that is similar to that involved with tumor, that involved with normal soft tissue, or whether it occurs by an entirely different pathway. To address this question, we have applied to abscess-bearing rats the same experimental challenges previously utilized in studies of the in vivo entry of Ga-67 into normal and malignant tissues (*2*).

We have previously proposed that Ga-67 is distributed between two plasma compartments. Plasma Compartment 1 (free Ga-67) routes the metal mainly to bone, excreta, and nonosseous tumor, whereas plasma Compartment 2 (protein-bound Ga-67) routes it to normal soft tissues (*2*). This scheme does not take into account reverse processes, and involves only the overall movement of Ga-67 in the initial phase of its biodistribution after intravenous administration. Under normal circumstances most of the Ga-67 present in the blood will be in plasma Compartment 2 (protein-bound Ga-67). We report here the results of experimental alterations of the binding of Ga-67 by plasma proteins (primarily transferrin) on the tissue distribution of Ga-67 in rats bearing an *S. aureus* abscess.

MATERIALS AND METHODS

Groups of five or more Fischer 344 rats* were used in these studies. Animals were matched as to sex and age ±2 wk. They had free access to food and water, but in each experiment food was withdrawn after Ga-67 ad-

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ministration in order to avoid any effects that might be produced by variations in food intake (*4*).

To produce abscesses, a saline slurry of rat liver that had been put through a 1-mm tissue press† was inoculated with *S. aureus* 6339‡ such that there were 100 million cells per milliliter. Use of the liver slurry served to keep the abscess localized. One-milliliter portions of this mixture were injected subcutaneously in rats on the back near the head. Abscesses and other tissues were then harvested on the fifth day after injection of the liver preparation.

All intravenous injections were made by tail vein. Gallium-67 citrate‖ was injected intravenously at a level of 20–50 μCi. In two studies, scandium citrate (0.5 mg Sc/kg) was injected along with Ga-67 and the animals were killed 4 and 24 hr later. In one study ferric citrate (140 μg Fe/kg) was injected intravenously 10 min before Ga-67 and the experiment terminated 5 hr after Ga-67 administration. In another iron study Imferon§ (25 mg Fe/kg) was injected intramuscularly 4 hr before Ga-67 and the animals were killed 24 hr following Ga-67 administration. When the effect of exogenous transferrin was to be investigated, rabbit apotransferrin (140 mg/kg) was injected intravenously 15 min before Ga-67 and the experiment was terminated 24 hr later. In studies of the effect of anemia, the animals were killed 24 hr after Ga-67 administration. The methods for producing anemia, rendering rabbit transferrin¶ iron-free, and preparing scandium citrate and ferric citrate have been reported previously (*1*,*2*).

Animals were killed by severing the aorta after light anesthesia with diethyl ether. Weighed samples of tissue were counted in a well scintillation counter against an aliquot of the Ga-67 used, and the Ga-67 concentration calculated as percent administered dose per gram of tissue normalized to a body weight of 250 g. Both the viable inflammatory and necrotic portions of the abscesses were sampled. Whole-body retention and total abscess uptake of Ga-67 were determined by the geometry-independent technique of Gibbs et al. (*5*). Results are expressed as the mean ±1 s.e. Statistical analyses were performed using Student's *t*-test.

RESULTS

Tables 1 and 2 show the results obtained at 4 and 24 hr after intravenous administration of Ga-67 and scandium. Contrary to the behavior observed with transplanted rat and mouse tumors (*1*,*2*), viable inflammatory tissue at both time periods showed a highly significant decrease in Ga-67 concentration that was similar to that observed with normal soft tissues. Intravenous administration of ferric citrate, and intramuscular administration of Imferon, again significantly decreased Ga-67 uptake in the *S. aureus* abscess and also that in normal soft tissues (Tables 3 and 4), although the decreases were less pronounced than those seen with scandium (Tables 1 and 2).

Since experimentally forcing Ga-67 into plasma Compartment 1 (free Ga-67) decreased Ga-67 uptake in both the abscess and the normal soft tissues, we then studied the effect produced by forcing Ga-67 in the reverse direction—toward plasma Compartment 2 (protein-bound Ga-67) by administering rabbit apotransferrin and by inducing anemia.

Administration of apotransferrin resulted in an increase in the uptake of Ga-67 by viable *S. aureus* abscess tissue; this paralleled that observed with normal soft

TABLE 1. EFFECT OF SCANDIUM ON THE 4-HR TISSUE DISTRIBUTION OF Ga-67 IN MALE RATS BEARING *S. Aureus* 6339 ABSCESSES*

Tissue	Control	Sc (0.5 mg/kg)	Significance P
	% Administered Ga-67/g		
Viable abscess	1.30 ± 0.08†	0.76 ± 0.03	<0.001
Necrotic abscess	0.38 ± 0.04	0.35 ± 0.04	—
Liver	0.75 ± 0.08	0.27 ± 0.01	<0.001
Spleen	0.83 ± 0.02	0.34 ± 0.02	<0.001
Lung	0.61 ± 0.01	0.19 ± 0.01	<0.001
Muscle	0.10 ± 0.01	0.02 ± 0.00	<0.001
Femur	0.81 ± 0.03	1.20 ± 0.16	0.02–0.05
Marrow	0.86 ± 0.05	0.13 ± 0.01	<0.001
Blood	0.96 ± 0.02	0.33 ± 0.03	<0.001
Ga-67 retention (%)	92 ± 0.4	69 ± 1.7	<0.001
Abscess wt (g)	2.1 ± 0.1	2.1 ± 0.2	—
Ga-67 in abscess (%)	3.3 ± 0.2	1.9 ± 0.1	<0.001

* Five animals per group.
† Standard error.

TABLE 2. EFFECT OF SCANDIUM ON THE 24-HR TISSUE DISTRIBUTION OF Ga-67 IN MALE RATS BEARING *S. Aureus* 6339 ABSCESSES*

Tissue	Control	Sc (0.5 mg/kg)	Significance P
	% Administered Ga-67/g		
Viable abscess	3.40 ± 0.15†	1.70 ± 0.10	<0.001
Necrotic abscess	0.26 ± 0.02	0.24 ± 0.04	—
Liver	1.30 ± 0.06	0.66 ± 0.03	<0.001
Spleen	2.30 ± 0.18	0.74 ± 0.07	<0.001
Lung	0.42 ± 0.08	0.20 ± 0.03	0.02–0.05
Muscle	0.14 ± 0.02	0.02 ± 0.00	<0.001
Femur	0.89 ± 0.09	0.98 ± 0.13	—
Marrow	1.90 ± 0.08	0.60 ± 0.05	<0.001
Blood	0.13 ± 0.00	0.14 ± 0.01	—
Ga-67 retention (%)	87 ± 1	65 ± 1	<0.001
Abscess wt (g)	2.6 ± 0.2	2.7 ± 0.2	—
Ga-67 in abscess (%)	6.6 ± 0.9	4.3 ± 0.2	0.02–0.05

* Five animals per group.
† Standard error.

tissues (Table 5). The increase in abscess Ga-67 concentration, although marginal in significance (P = 0.02–0.05), was nevertheless completely the reverse of the highly significant decrease (P <0.001) that we had previously observed in Ga-67 uptake in the Morris 5123C hepatoma with apotransferrin administration (*2*).

Induction of anemia, on the other hand, produced an unexpected but significant decrease in the Ga-67 concentration in viable abscess tissue (Table 6). This was similar to the effect previously observed with the Morris 5123C hepatoma (*2*) and contrary to that seen with the normal soft tissues in this experiment. A repeat study gave the same results.

DISCUSSION

Many suggestions as to the mechanism(s) involved in the uptake of Ga-67 by inflammatory lesions have been

TABLE 3. EFFECT OF FERRIC CITRATE ON THE 5-HR TISSUE DISTRIBUTION OF Ga-67 IN FEMALE RATS BEARING *S. Aureus* 6339 ABSCESSES*

Tissue	Control	Fe (140 μmg/kg)	Significance P
	% Administered Ga-67/g		
Viable abscess	1.60 ± 0.10†	1.30 ± 0.07	0.01–0.02
Necrotic abscess	0.24 ± 0.03	0.29 ± 0.04	—
Liver	0.93 ± 0.03	0.75 ± 0.02	<0.001
Spleen	0.82 ± 0.04	0.64 ± 0.05	0.01–0.02
Lung	0.68 ± 0.03	0.72 ± 0.02	—
Muscle	0.12 ± 0.01	0.10 ± 0.01	—
Femur	0.84 ± 0.03	1.00 ± 0.04	0.001–0.01
Marrow	1.20 ± 0.09	0.72 ± 0.06	<0.001
Blood	1.10 ± 0.03	1.30 ± 0.04	<0.001
Ga-67 retention (%)‡	95.0 ± 0.4	90.2 ± 0.7	<0.001
Abscess wt (g)	2.7 ± 0.3	2.5 ± 0.2	—
Ga-67 in abscess (%)‖	6.0 ± 0.6	5.4 ± 0.5	—
Serum Fe (μg/dl)	150 ± 4	370 ± 7	<0.001
Serum TIBC (μg/dl)§	330 ± 5	370 ± 10	0.001–0.01

* Ten animals per group.
† Standard error.
‡ Body retention at 4 hr; five animals only.
‖ Five animals only.
§ Serum total iron-binding capacity.

TABLE 4. EFFECT OF IMFERON ON THE 24-HR TISSUE DISTRIBUTION OF Ga-67 IN FEMALE RATS BEARING *S. Aureus* 6339 ABSCESSES*

Tissue	Control	Imferon (25 mg Fe/kg)	Significance P
	% Administered Ga-67g		
Viable abscess	2.20 ± 0.21†	1.40 ± 0.11	0.001–0.01
Necrotic abscess	0.33 ± 0.03	0.33 ± 0.05	—
Liver	1.40 ± 0.04	1.20 ± 0.05	0.001–0.01
Spleen	1.70 ± 0.07	1.20 ± 0.05	<0.001
Lung	0.42 ± 0.05	0.29 ± 0.02	0.02–0.05
Muscle	0.09 ± 0.01	0.09 ± 0.01	—
Femur	0.95 ± 0.04	1.00 ± 0.07	—
Marrow	1.40 ± 0.07	0.67 ± 0.07	<0.001
Blood	0.29 ± 0.03	0.30 ± 0.04	—
Ga-67 retention (%)	84.0 ± 1.0	78.4 ± 2.0	0.02–0.05
Abscess wt (g)	2.7 ± 0.3	2.4 ± 0.3	—
Ga-67 in abscess (%)	7.5 ± 0.8	4.9 ± 0.5	0.01–0.02
Serum Fe (μg/dl)	200 ± 5	440 ± 3	<0.001
Serum TIBC (μg/dl)‡	380 ± 6	440 ± 4	<0.001

* Ten animals per group.
† Standard error.
‡ Serum total iron-binding capacity.

made. These have ranged from increased capillary permeability (*6*) to association of Ga-67 with various proteins (*7,8*), polymorphonuclear leukocytes (*9*), siderophores (*10*), and infectious microorganisms (*11*). The consensus at present appears to hold that multiple factors are probably involved. This study, we believe, serves to point up the importance that should be placed on the binding of Ga-67 by plasma proteins, especially transferrin.

In this study with abscess-bearing rats, our results in four different biodistribution challenges—scandium citrate, ferric citrate, Imferon, and rabbit apotransferrin

TABLE 5. EFFECT OF RABBIT APOTRANSFERRIN ON THE 24-HR TISSUE DISTRIBUTION OF Ga-67 IN MALE RATS BEARING *S. Aureus* 6339 ABSCESSES*

Tissue	Control	Transferrin (140 mg/kg)	Significance P
	% Administered Ga-67/g		
Viable abscess	3.30 ± 0.16†	3.80 ± 0.15	0.02–0.05
Necrotic abscess	0.45 ± 0.04	0.50 ± 0.05	—
Liver	1.60 ± 0.06	2.30 ± 0.12	<0.001
Spleen	2.40 ± 0.14	3.20 ± 0.12	<0.001
Lung	0.40 ± 0.04	0.48 ± 0.02	0.001–0.01
Muscle	0.15 ± 0.00	0.15 ± 0.02	—
Femur	1.10 ± 0.04	1.20 ± 0.09	—
Marrow	1.80 ± 0.17	3.00 ± 0.19	<0.001
Blood	0.22 ± 0.01	0.21 ± 0.01	—
Ga-67 retention (%)	84.0 ± 0.7	84.0 ± 0.6	—
Abscess wt (g)	2.2 ± 0.0	2.0 ± 0.2	—
Ga-67 in abscess (%)	5.5 ± 0.8	5.5 ± 0.6	—
Serum Fe (μg/dl)	160 ± 2	160 ± 2	—
Serum TIBC (μg/dl)‡	370 ± 1	720 ± 3	<0.001

* Ten animals per group.
† Standard error.
‡ Serum total iron-binding capacity.

TABLE 6. EFFECT OF ANEMIA ON THE 24-HR TISSUE DISTRIBUTION OF Ga-67 IN MALE RATS BEARING *S. Aureus* 6339 ABSCESSES*

Tissue	Control	Anemia	Significance P
	% Administered Ga-67/g		
Viable abscess	5.80 ± 0.32†	2.70 ± 0.02	<0.001
Necrotic abscess	0.46 ± 0.06	0.21 ± 0.04	0.001–0.01
Liver	1.70 ± 0.10	3.80 ± 0.50	0.001–0.01
Spleen	2.20 ± 0.12	6.50 ± 0.53	<0.001
Lung	0.44 ± 0.03	0.25 ± 0.02	<0.001
Muscle	0.05 ± 0.01	0.04 ± 0.01	—
Femur	1.00 ± 0.05	0.91 ± 0.04	—
Marrow	1.70 ± 0.03	3.60 ± 0.16	<0.001
Blood	0.31 ± 0.03	0.18 ± 0.02	0.001–0.01
Ga-67 retention (%)	85.0 ± 1.2	87.0 ± 1.0	—
Abscess wt (g)	3.3 ± 0.2	3.6 ± 0.5	—
Ga-67 in abscess (%)	8.7 ± 0.3	6.3 ± 0.5	0.001–0.01
Serum Fe (μg/dl)	170 ± 4	57 ± 1	<0.001
Serum TIBC (μg/dl)‡	370 ± 4	510 ± 5	<0.001
Hematocrit (%)	43 ± 1	27 ± 1	<0.001

* Five animals per group.
† Standard error.
‡ Serum total iron-binding capacity.

administration, all aimed at manipulating the binding of Ga-67 to plasma proteins—indicate to us that the initial entry of Ga-67 into inflammatory lesions may occur by pathways that are similar to those of normal soft tissues. Each of these challenges produced the same effect on the uptake of Ga-67 in viable inflammatory tissue and normal soft tissues (Tables 1–5). Since the initial biodistribution of Ga-67 is controlled by the binding of Ga-67 to plasma proteins (*2*), we feel that an endocytotic process mediated by the binding of Ga-67 to plasma proteins may be the predominant pathway involved in Ga-67 uptake by these two types of tissue.

If endocytosis does constitute a predominant pathway for Ga-67 into normal and inflammatory tissues, we suggest that the major phagocytic agent involved in Ga-67 uptake by inflammatory processes may be the in-situ long-lived macrophages arising from the monocytes that enter inflammatory processes secondary to the initial pronounced influx of granulocytes. The fact that Swartzendruber and Idoyaga-Vargas (*12*) observed a high Ga-67 uptake in macrophages but a low uptake in granulocytes, even though both cell types showed similar phagocytic activities as measured by latex particle phagocytosis, supports this contention. Moreover, a predominant uptake of Ga-67 by the macrophages present in inflammatory lesions would explain the ability of such processes to concentrate Ga-67 in the presence of agranulocytosis (*13,14*). Furthermore, Ross (*15*) has shown that the number of monocytes present in healing wounds was similar to that of controls when sustained neutropenia was produced experimentally.

In a further study, however, when we increased the binding of Ga-67 to plasma proteins by induction of anemia (Table 6), abscess tissue showed a decreased Ga-67 uptake similar to that we had previously seen with tumor tissue (*2*) and contrary to that seen with normal tissues. It is possible that this apparent discrepancy between the effects produced by apotransferrin and anemia could have resulted from a secondary effect associated with experimentally induced anemia, i.e., a decreased macrophage population with a resultant decrease in Ga-67 uptake in the viable portion of the abscess, which could in turn more than override the effect of the increased transferrin level that was produced by induction of anemia (see TIBC in Table 6). We have obtained qualitative histological evidence that there is indeed a decrease in the abscess macrophage population in rats made anemic by our technique, compared with that seen in controls.

Based on the overall results we have obtained in this study together with the above considerations, it appears that the uptake of Ga-67 by inflammatory lesions is more closely related to the processes involved in its concentration in normal soft tissue than it is to those occurring in tumor tissue. Figure 1 shows a schematic model of two basic pathways that, we suggest, might be involved in the entry of Ga-67 into soft-tissue tumors, normal soft tissue, and inflammatory lesions. At normal body pH, free

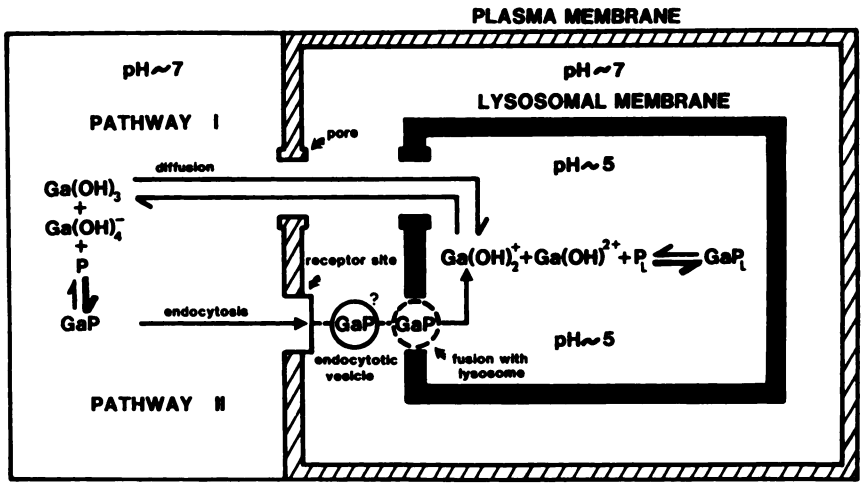

FIG. 1. Schematic model of two basic pathways that may be involved in uptake of Ga-67 by soft-tissue tumors, normal soft tissues, and inflammatory processes. No stoichiometric relationships should be inferred. It is suggested that soft-tissue tumor uptake of Ga-67 occurs mainly by Pathway 1, whereas that with normal soft tissues and inflammatory processes involves Pathway 2. The receptor site indicated in Pathway 2 is of the type described by Larson and co-workers (*16*).

gallium will be present primarily in the $Ga(OH)_3$ and $Ga(OH)_4^-$ mononuclear forms, whereas at an intralysosomal pH of 4–5, gallium will exist mainly as $Ga(OH)^{2+}$ and $Ga(OH)_2^+$ ions (*17,18*).

In view of these and our previous findings with tumor-bearing animals (*1,2*), we feel that the basic entry process associated with the uptake of Ga-67 by soft tissue tumors is by Pathway 1 (Fig. 1), while the uptake of Ga-67 by normal tissue and inflammatory lesions occurs to a major extent by Pathway 2. With tumor tissue, we feel that Ga-67 cellular uptake occurs mainly by passive diffusion of uncharged $Ga(OH)_3$ across the plasma and lysosomal membranes, followed by binding of Ga-67 to lysosomal proteins due to the lower intralysosomal pH and the consequent production of $Ga(OH)^{2+}$ and $Ga(OH)_2^+$ ions, in effect rendering the initial uptake process more or less irreversible (Fig. 1, Pathway 1). Gallium would thus be acting like a permeant, weak-base lysosomotrophic agent, as described by de Duve (*19*). On the other hand, with normal soft tissue and inflammatory processes, we suggest that the initial uptake of Ga-67 occurs mainly by some form of endocytosis, again with Ga-67 being ultimately bound by lysosomal proteins. Whether or not Ga-67 actually enters the cells of normal soft tissues and inflammatory lesions in a protein-bound form, or whether it is internalized at the receptor site (*16*) in some other form, is open to conjecture.

FOOTNOTES

* Harlan Industries, Indianapolis, IN.
† Harvard Apparatus, Milis, MA.
‡ American Type Culture Collection, Rockville, MD.
‖ New England Nuclear, N. Billerica, MA.
§ Lakeside Laboratories, Milwaukee, WI.
¶ United States Biochemical Corp., Cleveland, OH.

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