

## Acute Response to Elastase in Sheep Lungs Measured with Ga-67

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**The early inflammatory changes in sheep's lungs were studied with Ga-67 citrate, injected i.v. immediately following intrabronchial instillation of different doses of elastase into the right diaphragmatic lobes of 15 sheep. The elastase-induced lesions in the first five sheep (two received 4,000 units; three got 6,000) were imaged up to seven times in an 8-day period to measure the temporal changes in the lesion and to select the appropriate imaging time; the other ten sheep (800–8,000 units) were imaged once at 52 hr. Localization of Ga-67, as seen on the posterior and right lateral projections, was confined to a well-circumscribed region in the right lung field. The lesion could be detected as early as 4 hr after elastase instillation. It decreased to 60% of its initial area at 4 hr, while the total Ga-67 activity in the sheep remained constant after 52–75 hr. Gallium-67 uptake in the lesion correlated positively with the dose of elastase ( $r = 0.88$ ,  $p < 0.001$ ) and with the reduction in perfusion, as determined 4 wk after the elastase instillation ( $r = 0.66$ ,  $p < 0.05$ ). Early Ga-67 uptake in inflammatory lung lesions could therefore be used as a reliable predictor of the size of the acute elastase-induced inflammatory reaction, as well as of the sequelae involving the regional vascular supply 4 wk later.**

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It has been well documented that Ga-67, administered as citrate, accumulates in inflammatory lung lesions due to various etiological factors (1,2). Increased uptake of Ga-67 occurs in both localized and diffuse inflammatory processes such as the alveolitis of sarcoidosis (3–5), and in idiopathic pulmonary fibrosis (6).

The exact mechanism of Ga-67 accumulation at sites of inflammation is not known. However, hyperemia, increased capillary permeability, and decreased pH in the interstitial space are factors that favor Ga-67 accumulation (7–10). After i.v. injection, Ga-67 is believed to bind to transferrin and, when passing through the site

of inflammation, Ga-67 dissociates from the Ga-67-transferrin complex and is bound mainly to lactoferrin excreted by damaged polymorphonuclear cells (11). Direct binding of Ga-67 to bacteria has also been shown to occur (12).

Radionuclide imaging of Ga-67 has been widely used to assess the intensity and location of alveolitis in many interstitial lung diseases, including asbestosis (13,14), silicosis (3,13,15), sarcoidosis (3–5), and idiopathic pulmonary fibrosis (6). Line and his co-workers (6) have suggested the use of a Ga-67 index as a semiquantitative measure of Ga-67 uptake by the lung, taking into account the pattern, intensity, and extent of uptake, even though the cellular infiltrate may be markedly different. They have shown, for example, that the Ga-67 uptake in sarcoidosis is associated with activated alveolar macrophages and an accumulation of T lymphocytes

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within the alveolar structures (16,17). In contrast, the alveolitis of idiopathic pulmonary fibrosis is associated with the accumulation of neutrophils within the alveolar structures; neutrophils are involved in the localization of Ga-67 at sites of acute inflammation (16).

In sheep a panacinar emphysema model is being developed which facilitates an evaluation of the structural and functional lung changes occurring under well-controlled experimental conditions. Since Ga-67 imaging is used extensively as a noninvasive method to assess the extent and location of inflammatory lesions in the lungs, its use in studying the early inflammatory stages should facilitate an understanding of the pathogenesis of emphysema. The acute lesions were produced by the proteolytic degradation of lung elastin following the controlled intrabronchial instillation of elastase in doses previously shown to induce emphysema (18). The aims of this study were: (a) to measure the uptake of radioactive Ga-67 in the acute inflammatory lesion as a function of dose of administered elastase; (b) to measure the temporal changes in the acute lesion; and (c) to determine the relationship between the degree of the early inflammatory reaction and the resultant changes in lung function and structure measured 4 wk later.

#### MATERIALS AND METHODS

**Animals and elastase administration.** The study used 15 castrated male sheep of mixed Dorset and Cheviot strains, 5 to 14 mo of age and weighing between 27 and 52 kg. The animals were normal by physical examination, had normal hemograms and rectal temperatures, and were free of lung worms. Animal data and enzyme dose are given in Table 1.

Porcine pancreatic elastase (EC 3.4.21.11) was obtained commercially.\* A typical preparation contained 119 units of enzyme activity per mg. The total dose of elastase instilled in each sheep ranged from 800 to 8,000 units. Twenty-milliliter aliquots of elastase were instilled, through a fiberoptic bronchoscope under general anesthesia, into eight subsegments of the lower right lobe, as described in detail elsewhere (18). The left lung served as control.

**Gallium-67 imaging.** Six mCi Ga-67 citrate were injected i.v. into 15 sheep immediately after the instillation of elastase. Uptake in the resulting lesions was measured by imaging the lungs with a scintillation camera in the posterior and right lateral projections. Five sheep (two with 4,000 units and three with 6,000 units elastase each) were analyzed up to seven times in an 8-day period (at 4, 28, 52, 75, 100, 169, and 196 hr after injection, respectively) to follow the temporal changes in the acute lesion and select an appropriate imaging time. Based on these data, the other ten sheep were imaged once at 52 hr. Images of 1 million counts in each projection were stored in a computer. The Ga-67 distribution was imaged

TABLE 1. SHEEP AND ENZYME DATA

Sheep	Age (mo)	Wt (kg)	Elastase dose* (units)	Elastase concentration (units/ml)
545	12	27	800	5
508	12	43	800	5
507	12	52	2,400	15
521	12	34	2,400	15
548	13	33	4,000	25
490	13	33	4,000	25
603	13	39	4,000	25
606	12	43	4,000	25
538	9	32	6,000	37.5
522	14	35	6,000	37.5
568	5	32	6,000	37.5
594	5	28	6,000	37.5
595	5	28	6,000	37.5
541	13	31	8,000	50
544	12	27	8,000	50

\* A total of 160 ml (20 ml/subsegment) were instilled in 8 subsegments of the right diaphragmatic lobe in each sheep.

with a 400-keV collimator using a 50% window for the 93- and 185-keV photons (38.6 and 20.8% abundance, respectively). In two of the sheep (4,000 units) the net Ga-67 activity in the region of the lesion was determined after correcting for that in the blood in two different ways: (a) by i.v. injection of Tc-99m-labeled red blood cells for direct imaging of the blood pool in the lesion area; and (b) by subtracting the average Ga-67 activity per pixel in a normal left-lung region from the measured average Ga-67 activity per pixel in the inflamed right lung. In the first method, the same region of interest was used to determine the Ga-67 to Tc-99m ratio in the left lung, which was assumed to be the same as that in the circulating blood of both lungs. The Ga-67 activity was measured initially with both Ga-67 and Tc-99m energy windows, after which the Tc-99m-labeled RBCs were injected. After 10 min the Tc-99m activity was measured in the Tc-99m energy window and corrected for Ga-67 breakthrough. Similar measurements were made in the lesion area of the right lung. The Ga-67 activity in the circulating blood was determined from the product of the Tc-99m activity and the Ga-67-to-Tc-99m ratio of the left lung. The net Ga-67 activity in the lesion was then calculated from the difference between the total activity in the lesion and that in the blood. No significant differences were found between the two methods, except at 4 hr after elastase, when differences of 30% were found. Thus, for the later times (>4 hr), only the second correction method was used in the data analysis. Next, all measured Ga-67 activities were normalized to the number of counts in 1 min. All results were also corrected

for decay. Determination of lesion size is described in the Results section.

**Radionuclide imaging of regional lung perfusion and ventilation.** Regional pulmonary blood flow ( $\dot{Q}$ ) and ventilation ( $\dot{V}$ ) were measured, respectively, with Tc-99m-labeled albumin macroaggregates (MAA) injected i.v., and by continuous inhalation of the short-lived Kr-81m gas ( $T_{1/2} = 13$  sec). The animals were carefully positioned in sternal recumbency using a three-sided wooden frame to minimize body movement. The Tc-99m images were used to position the lungs in the field of a scintillation camera. The relative positions of frame and camera were carefully measured, so that they could be reproduced for the subsequent measurements. A 280-keV medium-resolution collimator was used, with window settings of 25% for Tc-99m (140-keV peak) and 15% for Kr-81m (190-keV peak).

The animals were intubated under ketamine analgesia and the cuffs were inflated to prevent air flow around the endotracheal tube. The tube was attached to a three-way nonrebreathing valve. A steady flow of 25 ml/min of air flowing through the Rb/Kr generator to elute the Kr-81m was mixed with room air inspired through the inlet valve port. The expired air left through the outlet valve port and was vented through a disposable plastic hose.

Krypton-81m ventilation images were obtained in the posterior and right and left lateral positions, and were interdigitated with Tc-99m perfusion images. Data containing 500,000 counts in each image were acquired for optimal information density and stored on magnetic tape.

The radiotracer distributions for each sheep were analyzed in a digital computer<sup>†</sup> and displayed in a  $64 \times 64$  matrix with a gray scale. The posterior and left and right lateral Tc-99m and Kr-81m images were normalized to 500,000 counts after 2-point smoothing. In order to locate lung regions with impaired  $\dot{Q}$  and  $\dot{V}$ , the lungs were divided into a series of 6.5- by 6.5-mm square areas (pixels), each representing activity in the underlying lung tissue. The relative activities of Tc-99m and Kr-81m in each pixel were then calculated by the computer and printed.

Each sheep served as its own control, since the radionuclide studies were carried out before (control) and 28-32 days after elastase instillation (postelastase). Furthermore, the left lung was unaffected by the enzyme (18) and served as an additional control during both measurements, against which the changes in the treated right lung could be related and quantified. The total activity of each of the tracers in the posterior projection was measured for 6.5-mm-thick transverse slices of lung, and individual slice-by-slice cephalad-caudad distributions in each lung were computed. The ratio of right-to-left lung activity in each transverse slice was calculated for the control and postelastase measurements, and plotted as functions of lung-slice position.

**Tissue preparation for morphometry.** The sheep were killed between 28 and 32 days after elastase instillation for assessment of the anatomical changes in the lungs. Procedures for fixative instillation, removal of the lungs, and preparation of the sections for morphometry have been described previously (18). Paraffin sections ( $6 \mu\text{m}$ ) were cut from each tissue block (total of six blocks per lobe), stained with hematoxylin-eosin, and examined at a magnification of  $\times 100$ . Ten fields (excluding large airways and blood vessels) were chosen at random from one section of each of the six blocks of treated (right lobe) and control (left lobe) tissue and measured for average air-space diameter (19). The data from all 60 fields were averaged and expressed as alveolar mean linear intercept ( $L_m$ ) for any given lobe. Standard deviations of the  $L_m$  among the six sections of any given lobe generally did not exceed  $\pm 3\%$  of the mean for untreated lung and  $\pm 12\%$  for enzyme-treated lung. The results were finally expressed as  $L_m$  of treated lobe minus  $L_m$  of control lobe from the same animal.

**Statistical analysis.** Correlations were obtained from a least-squares fit of the data, calculated by linear regression analysis. Statistical significance was determined by Student's t-test.

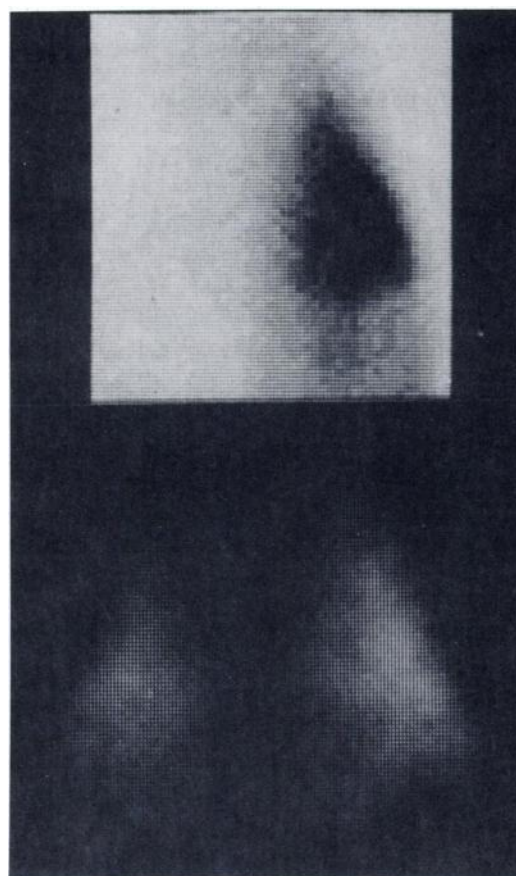
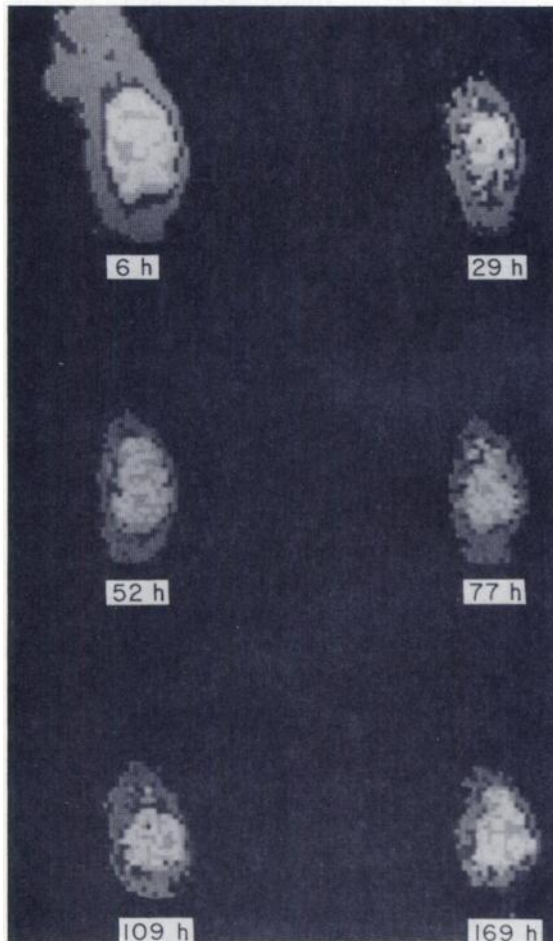


FIG. 1. Lung images of Sheep 490 showing Ga-67 localized in lesion in right diaphragmatic lobe (upper) and corresponding bilateral distribution of blood flow with Tc-99m MAA (lower) before enzyme instillation for comparison.

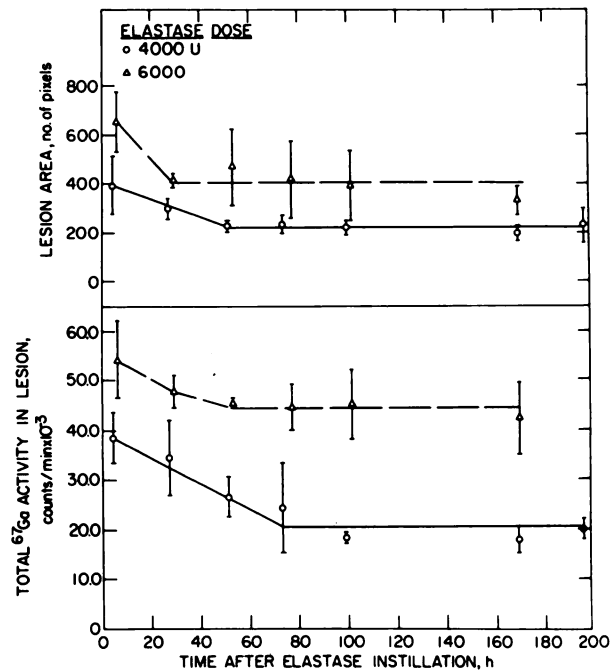


**FIG. 2.** Sequential Ga-67 images in Sheep 568, showing high-intensity core of activity surrounded by annulus of lower activity at indicated times after 6,000 units elastase instillation.

### RESULTS

**Temporal changes of Ga-67 activity in the lesion.** A localized lesion developed and was confined to the right lung, while the left lung and remaining right lung were unaffected (Fig. 1). The Ga-67 images changed significantly between 4 and 196 hr following elastase instillation in the five sheep studied (Fig. 2). The total activity in the lesion decreased to 53% of the 4-hr value between 4 and 75 hr, and to 83% of the 6-hr value between 6 and 52 hr for the 4,000 and 6,000-unit elastase doses, respectively, and then remained unchanged for all subsequent measurements (Fig. 3). At the same time, the lesion area, expressed as the number of pixels, decreased to an average of 56% of the 4-hr value between 4 and 52 hr, and to 62% of the 6-hr value between 6 and 28 hr for the 4,000 and 6,000-unit doses, respectively. The areas then remained unchanged for all subsequent measurements. Both lesion area and Ga-67 uptake were greater for the 6,000-unit than 4,000-unit elastase doses.

The Ga-67 image (Fig. 2) consisted of two distinct regions: a large inner region (core) of intense activity surrounded by an irregularly shaped, smaller annular



**FIG. 3.** Temporal changes in area (upper) and total Ga-67 activity (lower) in acute lesion. Lesion areas and their Ga-67 uptake were greater for 6,000-unit than for 4,000-unit elastase doses.

region of lower activity. The core consisted of any pixels that contained more than 60% of the maximum Ga-67 counts in a single pixel in the image; the annulus consisted of pixels that contained between 50 and 60% of the maximum Ga-67 counts in a single pixel in the image. The average core area increased from 55 to 69% of the total lesion area between 4 and 28 hr. The corresponding Ga-67 activity in the core increased from an average of 71 to 78% of that in the total lesion. No further changes in the relative core-to-total lesion values occurred after 28-52 hr.

**Correlation of initial Ga-67 uptake in the lesion with elastase dose.** Uptake of Ga-67 in the lungs was confined to a localized lesion in the right diaphragmatic lobe of each of the 15 sheep, and its total activity in the lesion measured at 52 hr correlated positively ( $r = 0.88$ ,  $p < 0.001$ ) with the dose of instilled elastase (Fig. 4).

**Correlation of regional lung function with initial Ga-67 uptake.** Since left (untreated) lung function remained unchanged during the 28-32-day interval between the control and postelastase measurements for all animals studied (18), and since Q and V abnormalities occurred only in the treated right lung, they were expressed as a ratio of the regional right-to-left lung activities of each tracer plotted as functions of lung-slice position in the posterior projections of each sheep. The ratio decreased below the control values with decreasing Q and V. The results were quantified by summing the ratios for each lung slice and then determining the overall difference between the control and postelastase values. This overall difference, expressed as a percentage of the control value,

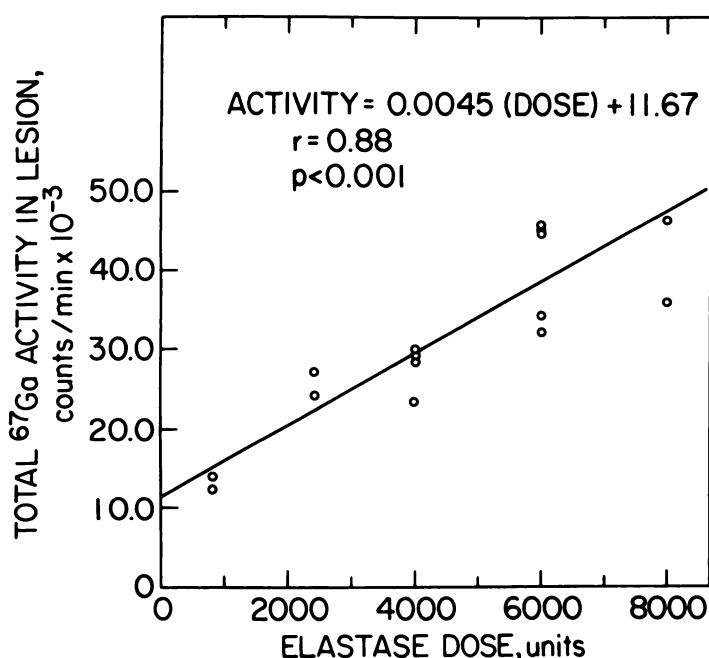


FIG. 4. Correlation of Ga-67 uptake in lesion with elastase dose for 15 sheep.

represented the change in function for each sheep caused by the instilled elastase (Table 2). A statistically significant correlation ( $r = 0.66$ ,  $p < 0.05$ ) was obtained between the change in Q, expressed in terms of the overall difference between the control and postelastase ratios of the right-to-left lung Tc-99m activities, and the Ga-67 uptake in the lesion at 52 hr (Fig. 5). Q decreased with increasing Ga-67 uptake. V also appeared to decrease, but the results did not attain statistical significance ( $r = 0.38$ ).

**Variation of mean linear intercept with initial Ga-67 uptake.** Alveolar enlargement and destruction of lung tissue (primarily panacinar) was found by microscopic examination of lung tissue from the enzyme-treated lung 28–32 days after elastase instillation.  $L_m$  increased from a mean ( $\pm$ s.e.m.) of  $0.064 \pm 0.001$  mm for the control lungs to  $0.102 \pm 0.008$  mm for the enzyme-treated lungs. The difference in the means of  $0.038 \pm 0.007$  mm was statistically significant by paired t-test ( $p < 0.001$ ). However, whereas  $L_m$  appeared to increase with increasing Ga-67 uptake, the results did not attain statistical significance ( $r = 0.33$ ).

DISCUSSION

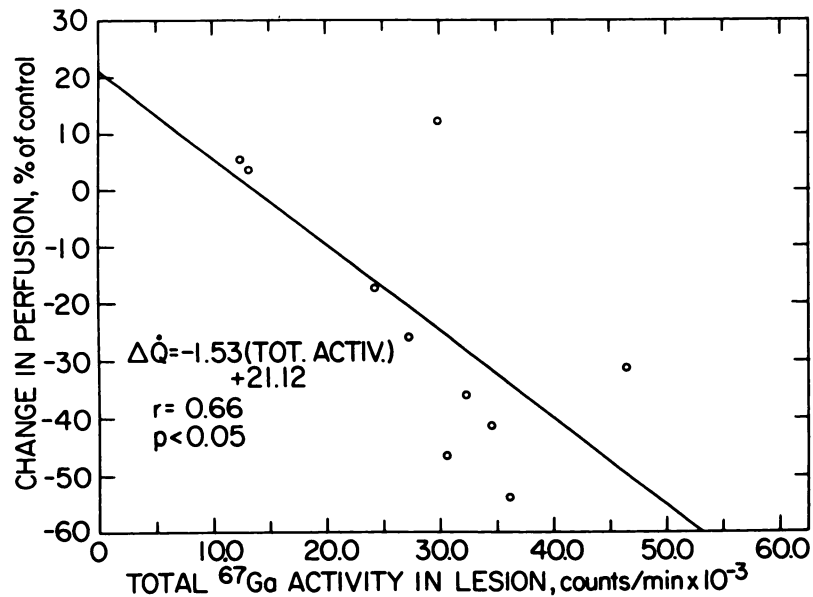
Gallium-67 uptake in the lungs of patients with interstitial lung disease is believed to reflect the degree of acute alveolitis (13). Therefore, imaging with Ga-67 is being utilized clinically to quantify the extent of the alveolitis and its anatomic location as a noninvasive method to follow the course of the disease and its response to therapy. Emphysematous-like lesions are produced in the lungs of experimental animals by the instillation of the proteolytic enzyme elastase (20,21).

Lesions have been produced in the rat, mouse, and hamster, as well as in the larger dog model (21–23). In the early stages following elastase instillation in these animal models, the lesion shows alveolar edema, hemorrhage, and exudation of polymorphonuclear leukocytes, which clears after several days (24). Weinberg and Hayes (25) also found widespread mitotic activity in the cells lining the airways and blood vessels of hamsters. The quantity of elastin in the lungs was markedly reduced within 24 hr after elastase instillation. Following this phase of acute injury, structural remodelling of the

TABLE 2. Ga-67 UPTAKE IN SHEEP LESIONS AT 52 hr

Sheep	Elastase dose (units)	Total Ga-67 activity in lesion (cpm $\times 10^{-3}$ )	Change in $L_m$ (mm)	Change in Q, (% of control)
508	800	12.5	0.028	5.5
545	800	14.1	0.011	3.8
507	2,400	24.2	0.008	-17.1
521	2,400	27.2	0.036	-25.8
490	4,000	30.5	0.050	-46.5
548	4,000	29.8	0.053	12.8
603	4,000	29.4	—	—
606	4,000	23.7	—	—
522	6,000	34.4	0.064	-41.1
538	6,000	32.2	0.095	-35.9
568	6,000	44.7	—	—
594	6,000	45.5	—	—
595	6,000	45.6	—	—
541	8,000	36.0	0.018	-53.9
544	8,000	46.3	0.032	-31.2

**FIG. 5.** Correlation of overall difference between control and postelastase ratios of right-to-left lung Tc-99m activities (decrease in perfusion) with Ga-67 uptake in lesion for 10 sheep. Difference in perfusion between control and postelastase measurements was computed for each 6.5-mm-thick lung slice, and expressed as ratio of right-to-left lung Tc-99m activity. Sum of differences for all lung slices in each sheep, expressed as percentage of integrated ratios for control measurements, then represents individual ordinates on this curve.



lung results in a diffuse lesion with the characteristics of human panacinar emphysema.

The sheep was selected for the present studies because the gross anatomical features of its lungs and tracheo-bronchial tree closely resemble those of humans. Furthermore, its large lung size facilitates the controlled instillation of enzyme into the preselected lung subsegments through a fiberoptic bronchoscope, and the subsequent measurement of regional distributions of the Ga-67 and the other radioactive tracers to determine Q and V with a scintillation camera. Repeated Ga-67 measurements were readily and reproducibly carried out. Unlike other studies reported previously (22,23), functional measurements were made before and 4 wk after elastase instillation. Each sheep therefore served as its own control. Furthermore, the left lung was unaffected by the enzyme and served as an additional control against which the changes in the treated right lung could be related and quantified.

Lesions were detected as early as 4 hr (initial measurement) after elastase treatment and changes in lesion size were found up to 52 hr. The time interval of 52 hr after elastase instillation was therefore selected for Ga-67 imaging in the remaining ten sheep. The 4-hr and 28- to 52-hr events were similar to the results obtained by Weinberg and Hayes (25) with Syrian hamsters. However, their finding, that the edematous and hemorrhagic changes had cleared completely by 8 days after injection, did not appear to be the case in our sheep, based on the relative annular area in the lesion. The sheep model may be closer to the dog than the smaller animals, since Niehaus and Reddan (22) found extensive vascular damage, as evidenced by gross hemorrhage, 7 days after elastase. This had cleared completely after 21 days. The Ga-67 in the lesion is believed to have been sequestered by tissue directly affected by the elastase

through enhanced protein-bound leakage and by accumulation in alveolar macrophages and perhaps other types of cells at the site of injury (14,25). Elevated Ga-67 activity in the irregularly shaped peripheral area in the early images was probably the result of reactive hyperemia (25), as well as some tissue inflammation resulting from direct elastase contact.

The correction for Ga-67 background in blood assumes a similar distribution of blood vessels in the two lungs. This was shown to be valid except for the initial (4-hr) measurement. At this time the inflammation in the right lung appeared to significantly increase the vascularity at the site of the lesion, as was also shown for the hamster (25), and this decreased with time due to healing.

Our results showed that the uptake of Ga-67 in the acute elastase-induced lesion at 52 hr correlated positively with the dose of instilled elastase. It also served as a predictor of the resulting reduction in Q. Similar trends were also suggested for the reduction in V and increases in L<sub>m</sub>, but the results did not attain statistical significance. Note that whereas 4 wk after enzyme instillation gives sufficient time for hamsters and rats to show near-maximal L<sub>m</sub> changes, elastase-induced emphysema in sheep has not been studied as a function of time after enzyme instillation or, for that matter, in any way previous to the present experiments. It may be that longer times are required in this longer-lived species for protease-mediated alveolar lesions to reach maturity. Such long-term studies in sheep are now in progress in our laboratories.

In conclusion, this study documents the sensitivity of lung imaging of sheep for Ga-67 uptake in the acute inflammatory lesion as a reliable, sensitive, and noninvasive means of quantifying the extent of inflammation in the acute elastase-induced lesion. Gallium-67 also

appears to be a useful predictor of the resulting functional and structural lung impairment found 4 wk later.

FOOTNOTES

- \* Elastin Products Co., Inc., Pacific, MO.
- † Digital Equipment Corp., Maynard, MA, VAX 11/780 system.

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