Direct Quantitation of Thoracic Gallium-67 Uptake in Sarcoidosis

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A method of direct quantitation of ^{67}Ga uptake in the lung is described. The attenuation coefficient requires calculation and is obtained simply for each patient by transmission using a planar radionuclide source. The validity of the method was tested with a phantom (error <10%). Forty-three patients with pulmonary and/or mediastinal sarcoidosis were classified. The different groups of patients as defined clinically and radiographically (controls, nonactive, and active sarcoidosis) were well-differentiated ($p < 0.001$).

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In the past, various studies have proved the usefulness of scintigraphic investigation using gallium-67 (^{67}Ga) in sarcoidosis. In diagnosis, it may show the extent of multisystemic spread (*1*) or the presence of characteristic disease locations (*2–4*). In disease assessment, active sites can be evaluated by means of ^{67}Ga uptake which may be clinically or radiologically undetected (*1, 5,6*). Furthermore, in therapy follow-up, relapse can be diagnosed or, when uptake persists, dosage shown to be inadequate (*7*).

The level of ^{67}Ga uptake appears to correlate with granulomatous activity (*5,7–9*). It is, therefore, important that accumulation be evaluated as precisely as possible. Nosal (*4*) was the first to our knowledge to attempt to do so. He defined four levels of activity and used the liver and the soft tissue of the shoulder as reference values. The first correlations with different activity markers [e.g., broncho-alveolar lavage (BAL), angiotensin converting enzyme serum level (ACE)] became possible with this qualitative method (*7,10*).

Another study by Line (*11*) used a technique which took into account the size of uptake areas and their respective activity levels (the liver was used as a reference). Van Unnick (*12*) assessed pulmonary and mediastinal activity by using the count rates recorded in regions of interest corresponding to those imaged on anterior and posterior chest scintigrams. He then compared the recorded activity with the radionuclide injected. The resulting classification of patients corresponded well with their radiological grading. The liver was not used as a reference and this method did not allow for the patient's own chest absorption.

The investigative works of Fleming, Macey and Thomas (*13–15*) on the quantitation of lung uptake following i.v. injection of technetium-99- (^{99m}Tc) labeled macroaggregates provides the basis for our method using ^{67}Ga. We propose a direct quantitation of ^{67}Ga uptake in the lung/mediastinum which takes patient attenuation of emission into account. The method, its validation in an experimental model, and the preliminary results obtained in a series of sarcoidosis patients are described.

METHOD

Theory

Consider a homogenous lung for which the ^{67}Ga linear attenuation coefficient is μ_2 and in which the radioactive tracer is uniformly distributed. A cylinder of this tissue, length L and unit cross-section, is placed perpendicular to the face of the gamma camera. Assume that anterior and posterior chest walls are of thicknesses a and b, respectively, and that the ^{67}Ga linear coefficient is μ_1.

The geometric mean (G) of the anterior and posterior count rates (Na and Np) is given by the equation:

$$G = (Na \cdot Np)^{1/2} = (E \cdot A/\mu_2) \cdot \exp(-\mu_1 \cdot (a + b)/2) \cdot (1 - \exp(-\mu_2 L)), \quad (1)$$

where E is camera/collimator system efficiency
and A (MBq/cm^3) the density of activity.

The attenuation correction for the lung and chest walls is derived from measurement of transmission. A planar radioactive source of ^{67}Ga is placed beneath the

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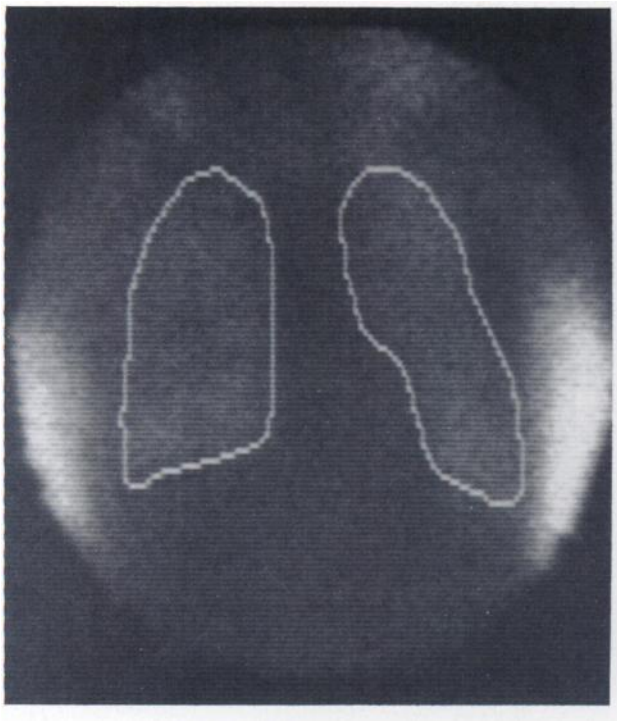

FIGURE 1
Transmission image (before i.v. of ^{67}Ga) determination of the pulmonary ROI; determination of total count Nt through patient in ROI

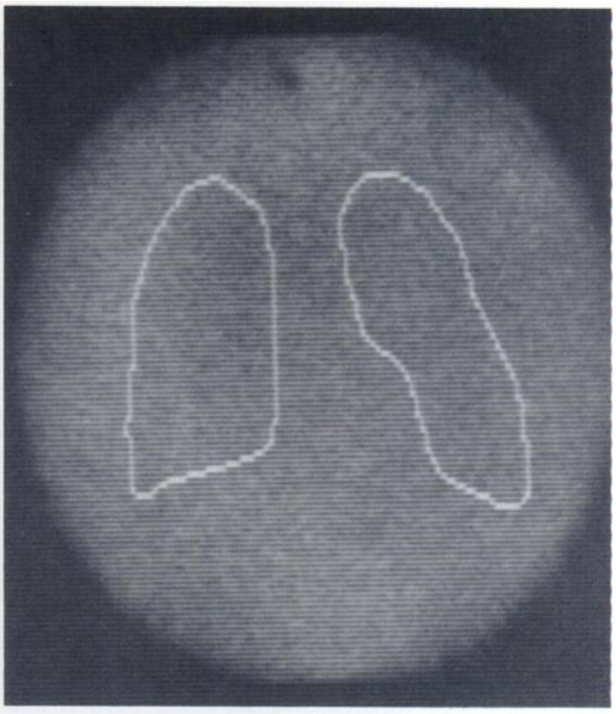

FIGURE 2
Determination of total count N_o obtained with source alone in pulmonary ROI (before i.v. of ^{67}Ga)

patient. Nt is the total count in the lung after passing through the patient (Fig. 1) and No the total count in the same region of interest, but from the source alone (Fig. 2).

The attenuation correction is then obtained by the equation:

$$(No/Nt)^{1/2} = \exp(\mu_1 \cdot (a + b)/2) + \mu_2 L/2). \quad (2)$$

When multiplying Eqs. (1) and (2), lung uptake is given by:

$$A \cdot L = G \cdot (No/Nt)^{1/2} \cdot (1/E) \cdot K \quad (3)$$

with

$$K = (\mu_2 L/2)/\sinh(\mu_2 L/2). \quad (4)$$

Fleming and Macey have shown that for lung <20 cm in thickness, when the coefficient K is 1, the error is <3% (in the case of ^{99m}Tc).

We therefore used Eq. (3) with K = 1 and checked the error for ^{67}Ga.

Experimental Validation

A model made of 1-cm-thick Plexiglas 20 × 20 × 15 cm^3 was used. Sawdust, which has a density close to that of lung parenchyma, simulates the lung. Water was mixed with the sawdust and then homogenized to increase the attenuation coefficient. For a given mixture of sawdust and water, an attenuation coefficient of No/Nt was obtained. This coefficient and the percentage of water contained in the sawdust were not correlated. A number of trials were carried out. For each trial, the water/sawdust mixture remained the same and so, consequently, did the No/Nt coefficient. The radioactive tracer was introduced progressively by means of a pipette and the whole was empirically homogenized. The tracer was measured by the activity meter and added in increasing doses of 8 MBq to 80 MBq for each trial. Successive values were obtained and for one value of No/Nt, a dozen values of activity measured-activity injected were acquired. Several examples are given in Table 1. Five trials were carried out for attenuation coefficient values ranging from 1.8 to 5.2. Absolute maximum error for the measurements was ~10%.

Protocol

Prior to i.v. injection of ^{67}Ga, the patient's transmission coefficient was calculated. A planar source (80 × 80 cm^2) containing ~2.5 mCi (100 MBq) of ^{67}Ga was

TABLE 1
Experimental Validation of Quantitative Method. Examples of Values Obtained with Phantom

	No/Nt	Injected activity (MBq)	Measured activity (MBq)
Trial 1	1.8	11.5	12.1
Trial 2	3.4	10.3	10.7
Trial 3	4.8	10.8	11.6
Trial 4	4.8	10.8	11.7
Trial 5	5.2	13.5	14.4

used. The patient lay on his back beneath a wide field-of-view gamma camera with a medium-energy, parallel hole collimator, interfaced to an image-processing unit MDS A2. The spectrometer was set at the two lowest peaks (93 and 185 keV) with a 20% window. The planar source was placed beneath the examination couch. Two recordings each lasting 10 min were made, one with the patient between the source and the gamma camera and the other with the source alone.

Two regions of interest (ROIs) were marked on the lungs and mediastinum, which were perfectly visible on the transmission image (Fig. 1). Two count rates were then recorded in these regions: Nt with the patient (Fig. 1) and No with the source alone (Fig. 2). The No/Nt ratio is then the patient's own transmission coefficient.

The actual scintigraphic examination was performed 72 hr after i.v. injection of ~38μCi (1.5 MBq) per kg of body weight. Six images of 5 min each were obtained: full-face and profile views of the head, and anterior and posterior views of the thorax and abdomen. The images were digitalized to a 128 × 128 matrix, stored and processed by the computer. Lung and mediastinal ROIs were determined on the anterior and posterior chest images (Figs. 3 and 4). A standard was placed 3 cm from the camera in a Plexiglas phantom and scanned for 5 min. The efficiency of the camera/collimator system (E in cps/MBq) was thus calculated. Following Fleming's equation, the absolute lung activity (Ap in MBq) was obtained. Ap was then compared with the injected activity and the percentage of ^{67}Ga uptake in the lung thus obtained.

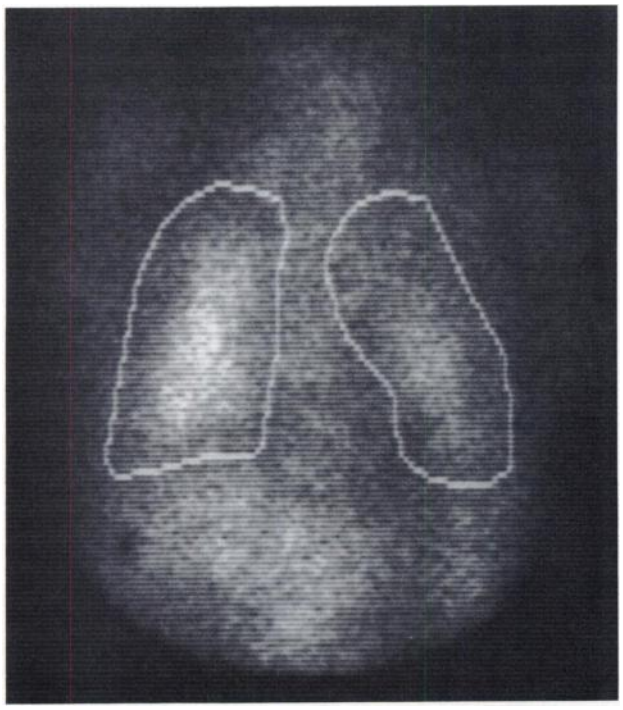

FIGURE 3
Gallium-67 scan (72 hr after i.v. of ^{67}Ga): determination of anterior total count Na in pulmonary ROI

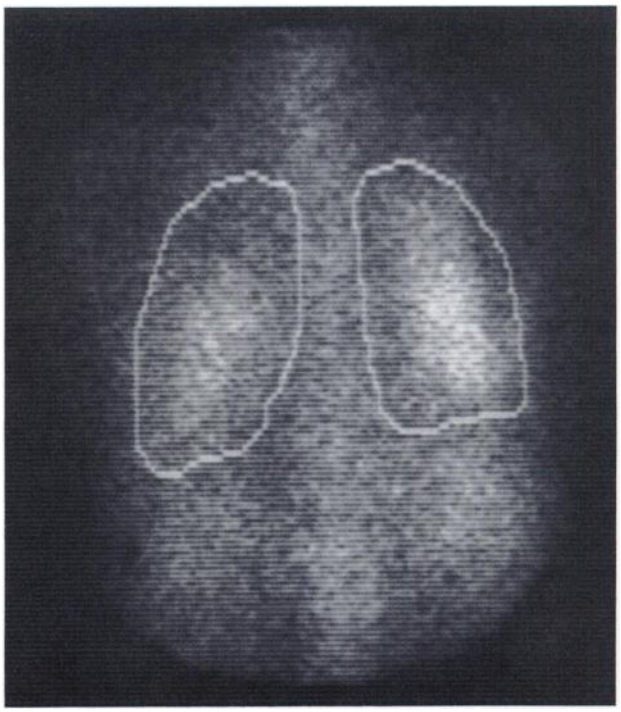

FIGURE 4
Gallium-67 scan (72 hr after i.v. of ^{67}Ga): determination of posterior total count Np in pulmonary ROI

PATIENTS

Scintigraphy was performed in 43 patients (27F, 16M; mean age 43 yr) suffering from pulmonary and/or mediastinal sarcoidosis. Diagnosis was based on clinical and chest x-ray findings confirmed in all cases by the presence of noncaseating granuloma on biopsies obtained mainly from bronchus or lung, lymph nodes or liver.

Larzul (*16*) attempted, on the basis of past experience, to classify sarcoidosis patients using clinical, radiographic, and functional data only (Table 2). Following his classification, we have investigated: (a) 14 patients with *active* sarcoidosis; (b) nine patients with spontaneously *inactive* sarcoidosis, either cured or in regression; (c) ten patients with *treated* sarcoidosis, all in complete remission; and (d) ten patients with *chronic* sarcoidosis or sarcoidosis of undetermined activity. Fourteen patients (eight men, six women) served as controls. They had been referred to the department for extra-thoracic (mainly abdominal) infection. Their chest radiographs were normal. We grouped (b), (c), and (d) together in a category of "*nonactive* sarcoidosis" for the correlation studies. The Mann and Whitney nonparametric test was used to compare the different groups of patients.

TABLE 2
Classification of Sarcoidosis Patients [Larzul (*16*)]

Groups of patients	Classification criteria
Active	Recent increasing cough Recent progressive dyspnea Systemic symptoms such as weakness, fever, arthralgia and erythema nodosum Impaired function of systemic localisations such as eyes, liver, heart, etc. . . Roentgenographic evidence of progressive disease Progressive impairment of pulmonary function tests (reduction of 20% of TLC and/or FEV_1/VC and/or DCLO values compared with baseline values considered as significant) Relapse forms
Treated	On steroids for at least 3 months
Chronic	All diseases sites considered as stable for at least 12 months
Inactive	All other forms with evidence of regression

RESULTS

Results are given in Tables 3 and 4 and Figs. 5–7.

The attenuation coefficient (No/Nt) for each group of patients (control, nonactive, and active sarcoidosis) lies between 2.5 and 5.5 (Fig. 5), which almost corresponds to the experimental range of coefficient values (see Experimental Validation). The No/Nt coefficient does not differ significantly from one group of patients to another. In three cases, the examination was repeated several months later and the No/Nt coefficient values had remained constant (Table 3). The first patient was referred for active sarcoidosis. His absolute lung uptake was 14% and his No/Nt attenuation ratio 5. He was seen 7 mo later. The scintigraphic images had spontaneously returned to normal and now showed an absolute pulmonary uptake level of 7% with more or less the same attenuation ratio: 4.7; the second patient was first seen after sarcoidosis had been diagnosed and corticosteroid therapy begun. His percentage of lung accumulation was 8.4% with an No/Nt attenuation coefficient of 4.6. He was seen 9 mo later. He was still under corticosteroids and presented a lung uptake of 8.7%. The No/Nt attenuation ratio had become 5, i.e., significantly nondifferent from his first value; the third patient was under treatment for cardiac sarcoidosis. The two examinations were carried out at an interval of 4 mo and with the patient under corticosteroids on both occasions. The level of lung uptake remained the same: 7.4%. The No/Nt coefficient attenuation was 3.8 and 4.2, respectively.

The distribution of lung uptake percentage values for the three groups (controls, nonactive, and active sarcoidosis patients) is given in Fig. 6 and the averages and standard deviations given in Table 4. The difference

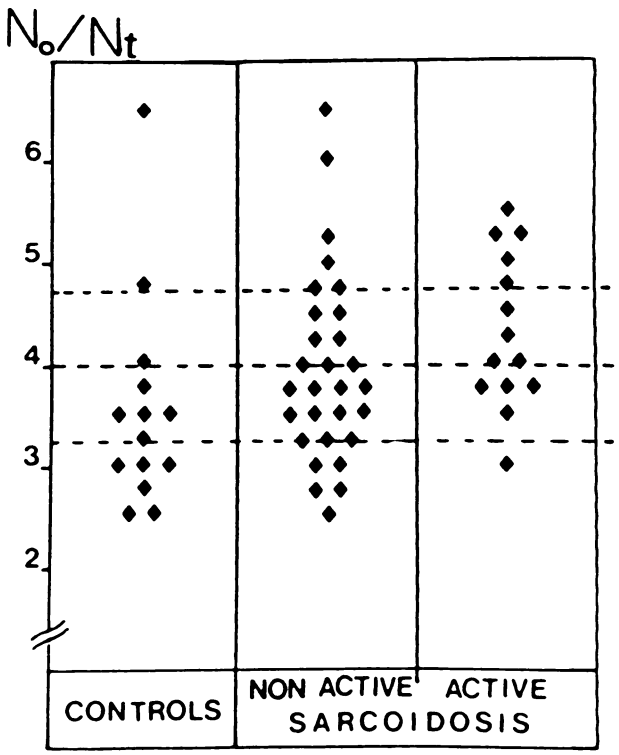

FIGURE 5
Attenuation coefficient No/Nt: values obtained for different groups of patients

between active and nonactive sarcoidosis values is very significant ($p < 0.001$). It must be noted that, scintigraphically, not all active sarcoidosis patients had intense lung activity [the grades ranged from 1 to 3, according to Nosal's classification (*4*)]. In all active sarcoidosis patients, however, the percentage of pulmonary accumulation exceeded 13%, i.e., it was greater than that of each control ($p < 0.0001$). The difference in distribution between nonactive sarcoidosis patients and controls is very significant ($p < 0.001$). In both populations, 80% of the patients presented a grade 0 scintigraphic image, following Nosal's classification (*4*). All nonactive sarcoidosis patients had a lung uptake of >6%.

Figure 7 presents the results obtained in pulmonary quantitation of nonactive sarcoidosis patients and dis-

TABLE 3
Gallium-67 Uptake in Lung. Results in Patients Who Underwent Two Examinations at Intervals of ~8 mo

	No/Nt coefficient	Lung uptake (%)
Patient 1	5	14
	4.7	7
Patient 2	4.6	8.4
	5	8.7
Patient 3	3.8	7.4
	4.2	7.4

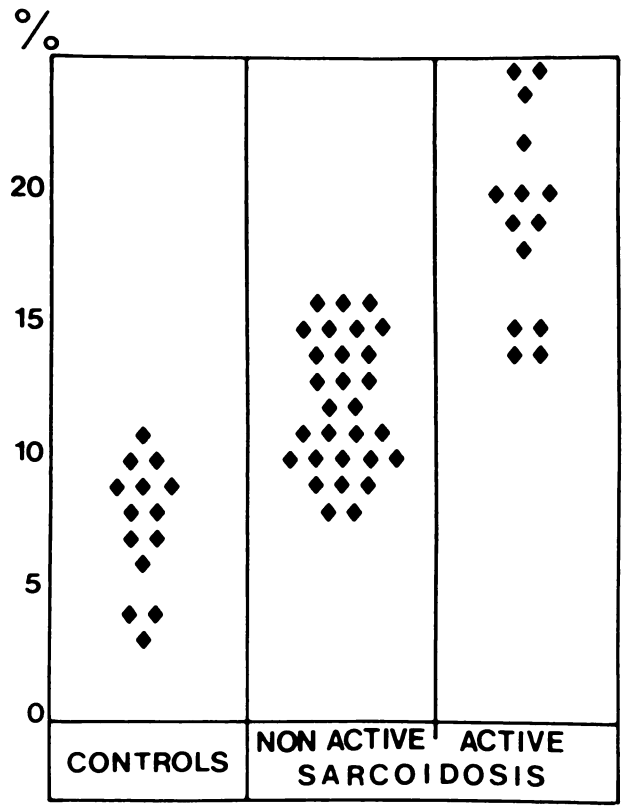

FIGURE 6
Direct quantitation method: percentage of thoracic ^{67}Ga uptake

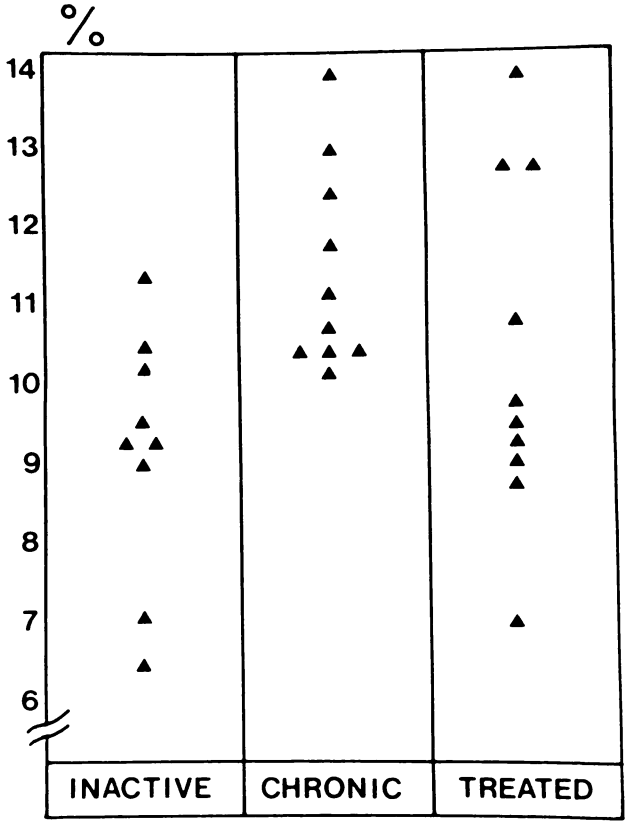

FIGURE 7
Direct quantitation method: percentage of thoracic ^{67}Ga uptake for nonactive sarcoidosis patients

tinguishes three groups: inactive sarcoidosis, chronic sarcoidosis, treated sarcoidosis (Table 2). A significant difference was found ($p < 0.01$) between the patients with an inactive form of the disease and those with a chronic form. Pulmonary uptake was >10% in all chronic sarcoidosis patients. On the other hand, the percentage of lung accumulation in treated patients ranged from 8 to 14% and distribution was not significantly different from that in chronic or inactive cases. Finally, when distribution in chronic and active sarcoidosis patients was compared, a significant difference was found ($p < 0.005$).

DISCUSSION

Gallium-67 scintigraphy has become important in diagnosing lung involvement in sarcoidosis patients.

TABLE 4
Gallium-67 Uptake in Lung. Average Values and s.d. per Group of Patients

Patients	n	Average	s.d.
Controls	14	7.75	2.60
Inactive sarcoidosis	9	9.25	1.60
Treated sarcoidosis	10	9.90	2.80
Chronic sarcoidosis	10	11.60	1.45
Nonactive sarcoidosis	29	10.30	2.25
Active sarcoidosis	14	17.95	3.90

Although Nosal's method (*4*) has made it possible for the first time to follow-up patients and to correlate with other activity markers (ACE, BAL) (*5,7*), it is, however, open to important criticisms: (a) only a crude evaluation of uptake at a particular site is possible, close correlation studies and the assessment of slight variations in uptake in the lungs in successive examinations are thus difficult; (b) the size of the sites is not taken into consideration and no distinction can be made between a small-sized localization and a diffuse spread of the same intensity; this is crucial where the lung is concerned; and (c) the reference value is the liver, but physiological hepatic uptake varies greatly from one person to another with the level of transferrin and lactoferrin in the blood, the coefficient of siderophillin saturation (*17*) and it can be modified by an intercurrent disorder (cirrhosis, hepatitis). Finally, sarcoidosis may localize in the liver itself.

Line (*11*) tried to improve quantitation principally by taking into account the size of abnormal uptake areas. With this method, differentiation between patients presenting diffuse forms and those presenting localized forms of the disease became possible (*18*). However, as the reference value was still the liver, the method can be criticized on the same grounds as above.

More recently, Van Unnick (*12*) suggested eliminating the liver reference by directly calculating the average

uptake on each lung as expressed as counts per pixel, per min, and per mCi injected. This method does not take into consideration patient attenuation and thus makes no allowances for morphological differences in patients nor for eventual changes in lung parenchyma due to the course of the disease (the increase in the No/Nt attenuation coefficient corresponds radiographically to the appearance of "a bright area").

The method presented in this paper seems to theoretically answer the above criticisms. The experimental validation was satisfactory. The artificial surroundings constituted by a mixture of sawdust and water is only an experimental representation of lung parenchyma. The absorption coefficients obtained in our series, however, are comparable to those of our experimental range (1.8 to 5.2). In our trials, [^{67}Ga]citrate distribution was somewhat inhomogeneous. In our opinion, this is an advantage, as it corresponds more closely to reality. The quantitation method described by Fleming and Macey (*13,14*) can, therefore, be used to study ^{67}Ga lung uptake. Although their method is not specific, we obtained results comparable to theirs during experimental validation with a phantom. The method could, of course, be extended to other isotopes currently in use in nuclear medicine, such as iodine-131 and indium-111 oxine, provided that it is limited to the study of lung uptake. The model presupposes a homogeneous environment with an attenuation coefficient μ_1 surrounded by two thinner homogeneous borders having a different coefficient, μ_2. The model mimics well a lung enclosed in a rib cage. The same would not apply if other common sites of ^{67}Ga uptake in sarcoidosis, such as the liver, spleen, and salivary glands, were to be studied.

Measurement of absolute uptake always requires a certain number of operative precautions. These should not, however, give the impression that the examination is too cumbersome for routine practice. The present method fulfills this condition. To determine the No/Nt transmission coefficient, No and Nt can be measured without modification of the geometric parameters. Only the patient should move between the two readings; the source, examination table, and camera should remain in position. It is important to note that the same spectrometric conditions apply to each measurement. Consequently, any eventual fluctuations have no effect on the overall result of the measurement of the ratio. In the same way, Na and Np are measured on the anterior and posterior scans at the same time as control activity is recorded. The $(Na \cdot Np)1/2 \cdot (1/E)$ ratio, therefore, contains no spectrometric errors. The homogeneity of the gamma camera must, of course, be verified to obviate any major errors in the overall evaluation of the No/Nt transmission factor. The amplification factor of the data acquisition system (E) must be defined for each examination. It is important that the anterior Na and posterior Np counts obtained from the scans and represented in counts per min be expressed in MBq. The method seems useful in the study of sarcoid patients.

It has already been shown that the No/Nt attenuation coefficient values do not differ significantly from one category of patients to another (Diagram 1). This tends to prove that fluctuations in the percentage of ^{67}Ga lung uptake between these different groups of patients are not due solely to a variation in the No/Nt coefficient. This coefficient allows for the patient's morphology and also for his specific lung density (normal lung, fibrosis, tuberculosis sequelae). It is, therefore, impossible to deduce how much of the emission attenuation is due to one or other of these factors. Consequently, it cannot be concluded that the patient has fibrosis of the lung simply because the attenuation coefficient has increased. On the other hand, a rise in the coefficient in the same patient during two successive examinations would be suspect. Such a case has not so far been encountered for the three different patients who underwent two investigations each (Table 3). Given these preliminary results, the method should reproduce well insofar as, in similar clinical conditions, pulmonary uptake percentages and attenuation coefficients were comparable. Furthermore, appreciable alterations in lung activity can be evaluated. In the first patient, a

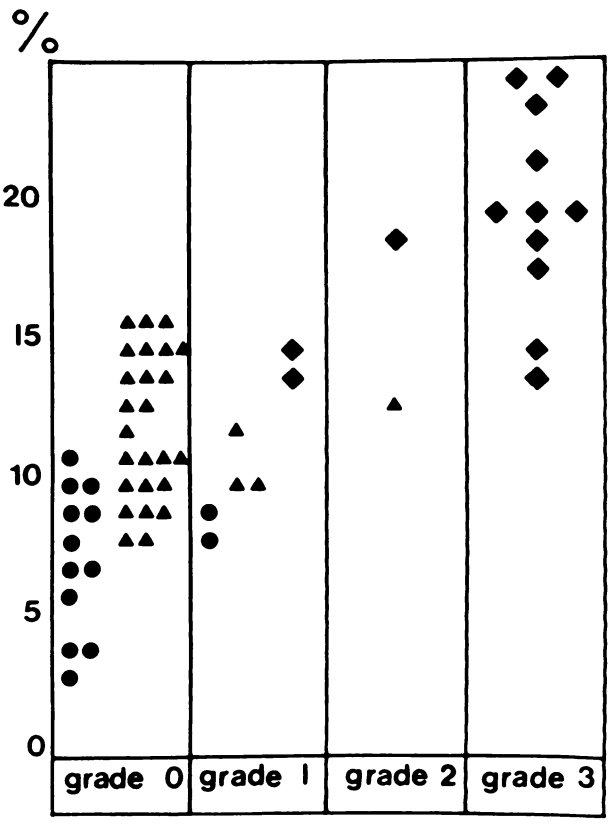

FIGURE 8
Comparison between NOSAL's qualitative method (*4*) and direct quantitation method. (●) Controls; (▲) Nonactive sarcoidosis patients; (◆) Active sarcoidosis patients

very significant drop in lung accumulation was noted when the disease went into spontaneous remission.

The values obtained by the quantitative method and those obtained by Nosal's analogical method were compared (Fig. 8). The first important fact is that the quantitative method does not provide additional information as regards patients with grade 2 or 3 lung activity. Almost all the patients concerned had active sarcoidosis. On the other hand, it is interesting to note that in patients with grade 1 pulmonary activity, the direct quantitation method classes the controls, the nonactive, and the active sarcoidosis cases in perfect order following the upward trend of the lung uptake percentages. As regards the patients with grade 0 lung activity (i.e., only the controls or the nonactive sarcoidosis patients), the absolute quantitation method discriminates satisfactorily between the controls and the patients with sarcoidosis.

CONCLUSION

It has been proved that ^{67}Ga scan is a good index of granuloma activity. The method of direct quantitation of pulmonary uptake described in this article presents the following advantages. First, the use of the liver as a reference value is no longer required (the pulmonary uptake is measured directly and compared with the total injected activity). Second, the attenuation specific to each patient is taken into account. Third, it is thus possible to obtain an absolute uptake percentage which is relatively close to reality.

This method is quite simple and easy to perform in all nuclear medicine departments. Our results demonstrate its value for physicians when uptake is low, as patients with sarcoidosis can be distinguished from normal controls. They allow a better classification of patients during diagnosis and follow-up.

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