# A Comparison between Monodisperse Tc-99m-Labeled Aerosol Particles and Kr-81m for the Assessment of Lung Function

M. D. Short, D. J. Dowsett, P. J. D. Heaf, D. Pavia, and M. L. Thomson

*University College Hospital and London School of Hygiene and Tropical Medicine, London, England*

***A quantitative method for study of the penetration and clearance of inhaled particles (5-micron Tc-99m-labeled polystyrene) in the human lung is described and compared with a Kr-81m technique for ventilation imaging. Volunteer healthy subjects and patients with chronic obstructive airway disease (COAD) were studied. Following inhalation of radioaerosol, data were recorded by a gamma-camera/computer system over a period of 6 hr. An aerosol penetration index (API) measures the proportion of aerosol reaching the peripheral region of the lung relative to that deposited in the larger central airways. A significant difference in the mean values of API for both groups was observed. Aerosol clearance rates from the whole lung and from central, intermediate and peripheral compartments of each lung field were studied. The healthy group showed a total clearance rate consistent with data from earlier work; the patients with COAD showed no clearance over the same period. Some healthy subjects were smokers, and differences in their penetration and clearance rates were evident, in spite of normal results from their conventional pulmonary function tests and Kr-81m ventilation studies. The aerosol technique, if carefully controlled, can be a more sensitive index for early lung abnormality than Kr-81m ventilation imaging.***

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The use of radioactive gases for the study of lung function is well established. Among the different gases available, Kr-81m has the distinct advantage of providing immediate dynamic ventilation images (*1,2*). Alternatively, inhaled radioactive particles have been used for lung function studies, and the deposition and clearance of these particles have been sensitive indicators of airway abnormality (*3–10*). Various heterodisperse aerosols have been used for this purpose (*8,10,11*), but control of particle size and manner of inhalation permits more valid quantitative comparison of total and regional lung function between subjects.

The radioaerosol used in this study is Tc-99m-labeled monodisperse polystyrene, administered under controlled conditions. A gamma-camera/computer system (*12*) was used to quantitate the initial deposition and subsequent clearance of the aerosol from the lungs. Before each aerosol study a regional lung ventilation image was obtained using a commercial Kr-81m generator*. Conventional pulmonary function tests ($FEV_1$ and FVC) were also performed.

This paper presents the results from a small group of subjects comprising a) healthy volunteers, including both smokers and nonsmokers, and b) patients with chronic obstructive airway disease (COAD). Various compartmental analyses were ap-

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For reprints contact: M. Short, Dept. of Medical Physics and Bio-Engineering, University College Hospital, 1st floor, Shropshire House, 11-20 Capper St. London WC1E 6JA, England.

plied to the radioaerosol lung images from this study, and one particular model is described that offers potential as an early diagnostic procedure.

## MATERIALS AND METHOD

**Krypton-81m ventilation scans.** The method described by Fazio and Jones (*2*) was used. Each subject was seated facing the gamma camera and inhaled the Kr-81m gas mixture using a face mask. After an equilibration period of 30 sec a 400,000-count anterior lung image was collected that, due to the 13-sec half-life of Kr-81m, reflected regional arrival of gas, i.e. ventilation.

**Radioaerosol production and administration.** The technique, which uses a spinning-disc aerosol generator (*13*), has been fully described elsewhere (*3,7*); it uses 5-micron (± 0.75) polystyrene particles tagged unleachably with Tc-99m (*14*). The volunteer subjects took eight controlled breaths of 800 $cm^3$ from a tank containing the aerosol. The average flow rate for each inhalation was monitored and the subject held his breath for 3 sec after each inhalation. The exhaled air was passed through a filter† to trap expired particles. Following removal of aerosol from the oropharynx by mouthwashing and gargling, the subject was seated facing the gamma camera, the average delay between final inhalation and first gamma image being 16 min. Anterior views of the subject's lungs were taken at regular intervals during a study period of 6 hr. Approximately 300 μCi were inhaled and a fixed data-collection time of 10 min was sufficient for adequate counting statistics (100,000 counts total). A parallel-hole, low-energy collimator was used for both the Kr-81m and radioaerosol investigations.

**Analysis of radioaerosol data.** Each lung field was divided into central, intermediate and peripheral regions, whose shapes are shown in Fig. 5 (inset). The regions are proportionally equal between subjects and depend on the total area of each lung field. The vertical edge of (II) bisects the lung field and (I) bisects this again. The horizontal axes were placed according to sternal notch and xiphisternum reference points. The major contribution in area (I) comes from the first few generations of bronchi. The intermediate area (II) includes the medial section of the bronchial tree, whereas the peripheral area (III) represents the small-airway region of the lung. By careful selection of the regions of interest, counts due to radioaerosol appearing in the stomach were excluded from areas of the left lung. In a few large subjects a small basal area of the peripheral lung region was not seen because of the limited size of the gamma camera's field of view. In these cases an additional image of the basal area was obtained, enabling a count correction to be made.

*Aerosol Penetration Index.* The counts recorded shortly after inhalation were used to calculate the Aerosol Penetration Index (API), which is taken as a measure of airway patency. The API for each

**TABLE 1**

| | | | | $FEV_1$ | | FVC | | $FEV_1/FVC$ | PFR | |
|---|---|---|---|---|---|---|---|---|---|---|
| Subject | Sex | Age | Height (m) | Observed | Predicted* (%) | Observed | Predicted* (%) | Observed | Observed | Predicted* (%) |
| *Nonsmokers* | | | | | | | | | | |
| H 1 | M | 53 | 1.90 | 4.64 | 117 | 5.89 | 115 | 79 | — | — |
| H 1 (Repeat) | | | | 4.74 | 116 | 5.95 | 116 | 80 | 550 | 92 |
| H 2 | M | 23 | 1.82 | 5.18 | 115 | 5.21 | 97 | 99 | — | — |
| H 3 | M | 32 | 1.80 | 4.91 | 118 | 6.20 | 123 | 79 | 630 | 101 |
| H 4 | M | 27 | 1.73 | 4.35 | 109 | 5.00 | 103 | 87 | 583 | 96 |
| H 5 | M | 39 | 1.82 | 5.56 | 137 | 6.71 | 134 | 83 | 640 | 105 |
| Mean values | | 38 | 1.82 | 4.89 | 118 | 5.82 | 114 | 85 | 600 | 98.5 |
| *Smokers* | | | | | | | | | | |
| H 6 | M | 66 | 1.82 | 4.25 | 129 | 6.09 | 138 | 70 | — | — |
| H 7 | M | 24 | 1.69 | 4.30 | 108 | 5.85 | 126 | 74 | 550 | 91 |
| H 8 | M | 37 | 1.80 | 3.68 | 91 | 4.95 | 100 | 74 | 580 | 95 |
| Mean values | | 42 | 1.77 | 4.07 | 109 | 4.29 | 121 | 73 | 565 | 93 |
| *Patients* | | | | | | | | | | |
| O 1 | M | 48 | 1.75 | 2.37 | 70 | 4.30 | 97 | 55 | 330 | 56 |
| O 2 | M | 66 | 1.76 | 0.82 | 27 | 2.16 | 53 | 38 | 147 | 28 |
| O 3 | M | 65 | 1.65 | 1.19 | 44 | 3.82 | 108 | 31 | 167 | 34 |
| O 4 | M | 60 | 1.78 | 2.20 | 69 | 4.28 | 98 | 51 | 265 | 43 |
| O 5 | F | 66 | 1.61 | 1.32 | 68 | 2.17 | 88 | 61 | 166 | 35 |
| Mean values | | 61 | 1.71 | 1.58 | 56 | 3.35 | 89 | 47 | 215 | 39 |

* Cotes 1975 (Reference 29)

lung is defined as a ratio of peripheral-area counts ($C_{III}$) to central-area counts ($C_I$) in the first lung image, so that:

$$API = C_{III}/C_I$$

*Whole lung clearance.* The clearance of radioaerosol from the whole lung field (I + II + III) during the study time was monitored for both groups of subjects and was compared with other techniques using scintillation probes (*3,7,15,16*). The data from each lung image were corrected for radioactive decay and expressed as percentages of the initial whole-lung count.

*Regional lung clearance.* In both groups of subjects the counts from areas (I), (II), and (III) were expressed as percentages of the initial total count from each lung. These percentages were then plotted against time after inhalation to show individual regional clearances.

## RESULTS

Table 1 shows the physical characteristics and lung-function indices for eight healthy subjects (H1 to H8), comprising five nonsmokers and three smokers, and five patients (01 to 05) with varying degrees of airway obstruction. All subjects were studied using Kr-81m and radioaerosol. Each subject was under continuous observation and did not smoke for 1 hr before or during either study. The five patients with COAD were receiving bronchodilator medication. One healthy subject (H1) had a repeat study. The mean Average Flow Rates obtained during the aerosol inhalation were 49 l/min (± 12.3 s.d.) for the healthy group and 43 l/min (± 4.7 s.d.) for the patients; these values are not significantly different.

Figure 1 shows a histogram of the mean API values (± 1 s.d.) for three groups: a) healthy nonsmokers, b) asymptomatic smokers, and c) patients with varying degrees of COAD. There are significant differences for both lungs between the healthy nonsmokers and the patients with COAD ($p < 0.01$; $t = 4.2$). The healthy nonsmokers and the smokers also showed differences in their mean API values. With the small numbers involved, however, only the right lung showed a significant difference in API value ($p < 0.05$; $t = 2.7$). The Kr-81m ventilation scans for all subjects in the healthy group were reported normal, and the lung-function indices shown in Table 1 for the nonsmokers and smokers were within normal limits.

Figure 2A shows the initial radioaerosol scan and the Kr-81m scan for one of the healthy nonsmoking subjects (H1, Table 1). The aerosol scan was performed 10 min after the final inhalation and contains 100,000 counts. It shows a typical deposition pattern for normal airways, with the major bronchi seen as areas of increased deposition and with a gradation toward the smaller airways in the peripheral region. The Kr-81m ventilation scan contains

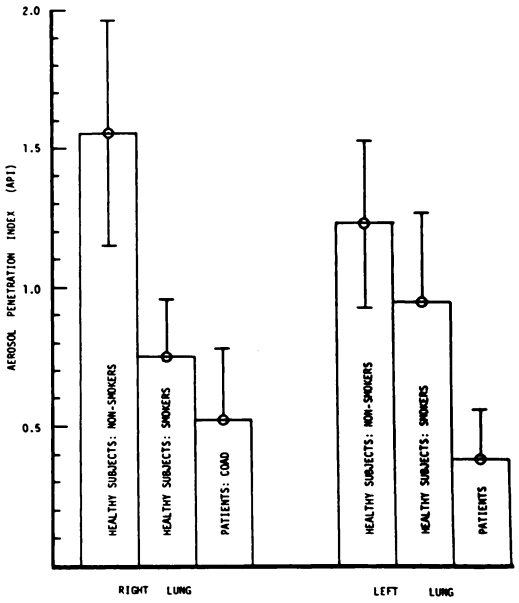


**FIG. 1.** The mean values (±1 s.d.) for aerosol penetration index (API) obtained from right and left lungs separately. Three groups are represented: Healthy smokers and nonsmokers (volunteers) and patients with chronic obstructive airway disease. A significant difference ($p < 0.01$) exists between patients and normals in all cases; smokers and nonsmokers are significantly different for the right lung only ($p < 0.05$).

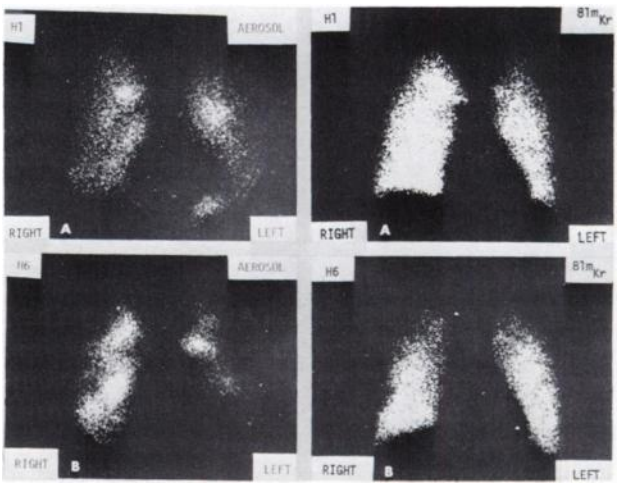


**FIG. 2.** Anterior radioaerosol and Kr-81m scintigrams for a nonsmoker (A) and an asymptomatic smoker (B), taken from healthy subjects used in this study (H1 and H6, Table 1.). Radioaerosol images contain approximately 100,000 counts collected over a fixed period of 10 min. Both images were taken 10 min after inhalation. Kr-81m images contain 400,000 counts and were obtained after a 30-sec equilibration period.

400,000 counts and is a typical normal. Figure 2B shows aerosol and Kr-81m scintiscans for one of the asymptomatic smokers in the healthy group (H6, Table 1). There are indications of a more central deposition than in Figure 2A, and the calculated value for the API (0.51) is significantly different ($p < 0.05$) from the mean value for the healthy nonsmoking group. The Kr-81m ventilation scan was judged clinically normal.

Figure 3 shows aerosol and Kr-81m scintigrams taken from two patients with COAD (03 & 05, Table 1). The aerosol images were performed about 10 minutes after the last inhalation. Both show abnormal deposition patterns, with a much larger proportion of retained aerosol in the major bronchi and less in the respiratory region. The Kr-81m scintigrams, although abnormal, reflect the degree of abnormality to a lesser extent. For all the patients with COAD studied, the API values were significantly different from the normal range, and the aerosol image itself was more clearly abnormal than the corresponding Kr-81m ventilation image.

In Figure 4, aerosol clearance curves (mean ± 1 s.d.) for the left and right lung fields of the nonsmoking subjects are shown, together with individual measurements from smokers and patients. During the 6-hr study period there was no evidence of clearance in any patient with COAD. However, total lung clearance for asymptomatic smokers followed the normal range (*7*). Gamma-camera data from one patient (04, Table 1) were compared with results obtained 11 mo earlier from a separate study using a probe detector system. Similar clearance characteristics were seen, allowing for differences in inhaled volume; both studies showed lack of mucociliary function.

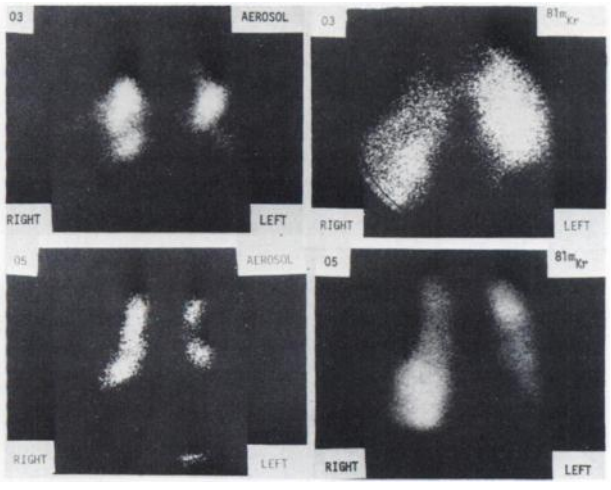


**FIG. 3.** Anterior radioaerosol and Kr-81m scintigrams for patients with COAD (03 and 05, Table 1). Aerosol and krypton scans were collected in a manner similar to those shown in Fig. 2. Concentration of aerosol in central regions typifies these COAD patients; krypton ventilation studies do not show such dramatic differences.

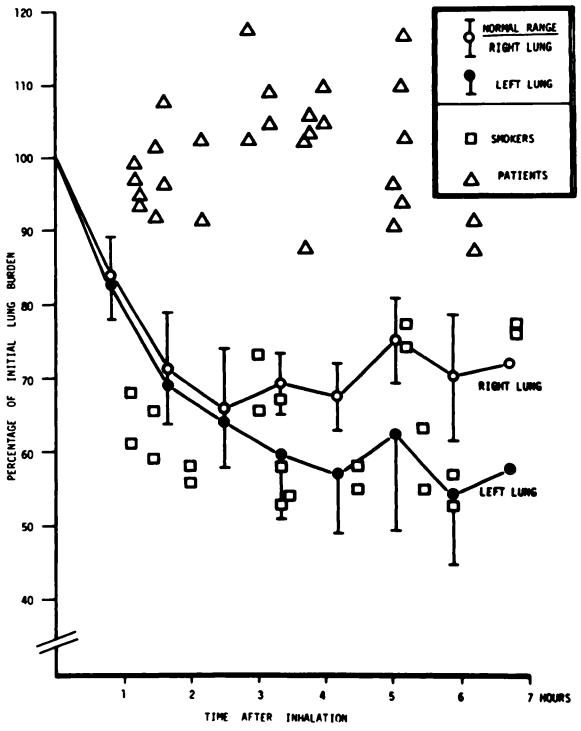


**FIG. 4.** Graphs showing normal (nonsmoker) total clearance for both left and right lungs (mean ± 1 s.d.). Normal left lung shows faster clearance ($F < 0.01$). Individual results are shown for smokers (□) and subjects with COAD (△). Smokers show no abnormality in their clearance rates, whereas COAD patients show no clearance at all over the 6-hr period.

In Figure 5 the counts in areas (I), (II), and (III) are shown as percentages of the individual lung count taken directly after aerosol inhalation. For clarity, in each area normal range (mean ± 1 s.d.) refers to the summed counts from both lungs. For asymptomatic smokers and patients with COAD, the data are shown as individual points. Aerosol clearances from areas (I) and (III) in the COAD group are different from the normal range—indeed, no clearance was observed in these subjects. The apparent absence of clearance in area (II) for the normals is caused partly by a balance in aerosol transport from peripheral to central region. Significant differences exist in the central and peripheral clearance rates between patients and normals during the 6-hr period. In both Fig. 4 and the central-region curve (I) of Fig. 5, the normal clearance curves show an initial fast phase, occupying the first 2 hr, followed by a slower phase.

The asymptomatic smokers (●) give deposition abnormalities in both regions (I) and (III), the latter region also showing a difference in clearance rate.

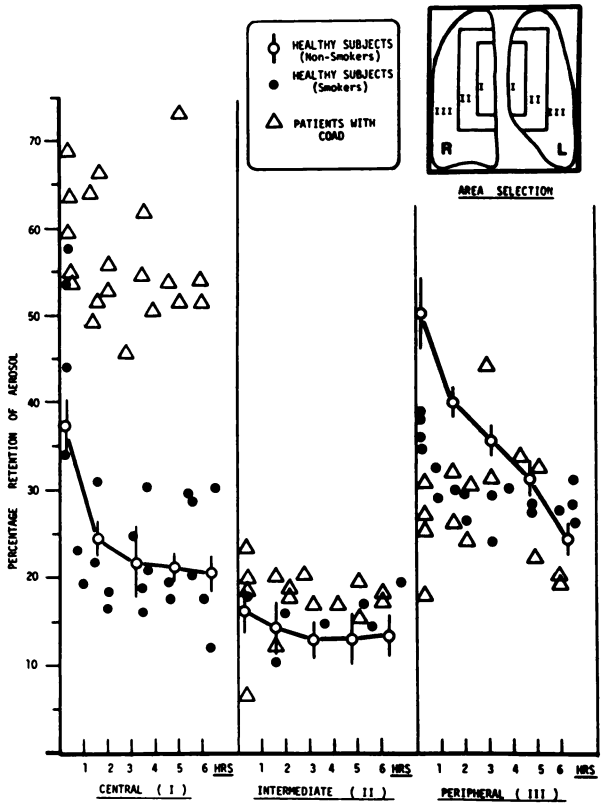


**FIG. 5.** Graphs showing percentage normal retention of aerosol in central (I), intermediate (II), and peripheral (III) lung regions (mean ± 1 s.d.) Values of first data points shown for peripheral region (III) clearly demonstrate the increased penetration in nonsmoking subjects. Both smokers (●) and patients with COAD (△) fall below this normal range. Central (I) clearance rates are similar for smokers and nonsmokers, but COAD patients show no clearance. Clearance information from intermediate region is of limited value.

The smokers tend to have deposition patterns that are more central, with a corresponding reduction in aerosol penetration to the peripheral region.

## DISCUSSION

Evidence to date indicates no toxic effects because of polystyrene aerosol in the alveolar regions; the 5-micron particle size should not impair local tissue growth.

The possibility of cytotoxic reaction has been discussed (*17*) and adverse reaction is unlikely when submilligram amounts are introduced into the human lung. With our technique, eight inhalations of 800 $cm^3$ containing 200 particles per cubic centimeter are used, giving a maximum deposition of 80 micrograms of polystyrene. Radiation dose was calculated from the assumption that healthy subjects clear 30% of the initial aerosol burden within 5 hr, leaving the remainder clearing at a much slower rate. Assuming a lung mass of 1 kg and a maximum activity of 500 $\mu$Ci inhaled, the lung radiation dose is calculated to be 230 millirads. Patients with clearance failure would have an estimated dose of 290 millirads. Radiation dose from a Kr-81m study was less than 10 millirads.

The physical parameters controlling the penetration of inhaled particles differ from those of a gas. Aerosol deposition in the human lung depends on a) physical properties of the aerosol (*18–20*), b) mode of inhalation (*21,22*), and c) degree of airway obstruction (*22*). Both (a) and (b) were rigorously controlled in all subjects, thus ensuring that differences in deposition relate only to airway abnormality. Although the aerosol penetrates toward the terminal bronchioles, the initial deposition pattern is not a ventilation image, since alveolar regions are not fully visualized. Airflow resistance in the smaller airways, however, considerably influences the deposition pattern.

The use of the short-lived Tc-99m may restrict clearance study times to a few hours when the gamma camera is used. Clearances over 24 hr using aerosols tagged with longer-lived radionuclides have been studied (*5,9*), and a measure of aerosol penetrance that relates initial deposition to retention in the peripheral area at 24 hr has been described (*9*). Our Aerosol Penetration Index (API) relates only to aerosol deposition immediately after inhalation, which may be more useful clinically. The regional concentrations measured here show that aerosol deposition and clearance in the lung periphery are sensitive indicators of early lung damage. Total clearance figures for right and left lung fields are less useful, since localized defects may be missed.

Some workers have described methods using radioactive gases to delineate the lungs and provide lung-volume corrections to radioaerosol data (*6,9*). The accuracy of these corrections depends on the variation in sensitivity caused by differing gamma-ray energies and the extent to which the gas image reflects lung volume. The energy of Kr-81m (190 keV) is more suitable for such a correction, although the image obtained is strongly influenced by ventilation. For this reason no correction for lung volume was applied in this study. The Kr-81m scans collected by the computer, however, were found useful for the delineation of lung outline in patients with predominantly central aerosol deposition. Transmission scans may be best for regional lung-volume correction (*23*).

When Kr-81m is used for lung function studies, gas diffusion that occurs within the lung may obscure the true ventilation picture. Diffusion is less significant with the size of aerosol used in this study, and the deposition images obtained directly

after inhalation reflect airway patency more accurately.

In the present study there was a marked difference in aerosol clearance between the healthy subjects and patients with COAD. The main clearance curve for the healthy subjects indicated that 37% of the initial lung burden was cleared after 6 hr. This is in good agreement with data previously reported using a probe system (*7*), but there was no evidence for clearance over the same period in patients with COAD studied here. This contrasts with earlier work (*3,7*) using probe detectors, which measured faster clearance in patients with COAD than in healthy subjects. This is attributed to a more central deposition in COAD, but absence of clearance over several hours has been observed in some bronchitic patients by other workers (*4,24*). The different geometrical detection efficiencies of gamma-camera and probe systems may partly explain this conflicting evidence. Productive coughing may well account for early clearance observed in some bronchitic patients (*24*). In this study some delay (mean 16 min) between inhalation and gamma-camera imaging was unavoidable. Nevertheless, examination of the initial lung scintigrams gave no indication of early clearance into the stomach. Recent work, in which the time delay is reduced to less than 2 min, has confirmed this finding.

Despite the limited subject material, significant effects caused by smoking were observed. Reduced values for API were obtained in asymptomatic smokers with normal pulmonary function tests and Kr-81m scans. No significant difference in total lung clearance between healthy smokers and nonsmokers was measured, in agreement with previous workers' results (*15,28*). Potential clinical applications of regional clearance measurements (Fig. 5) could include estimation of bronchodilator efficiency (*24,25*), efficacy of mucolytic agents (*16, 26,27*) and more detailed studies concerned with smoking (*5,15,28*). It is hoped that further investigation will reveal valuable diagnostic indices for early lung disease.

## CONCLUSION

The use of monodisperse radioactive aerosols for investigation of obstructive airway disease has been described and compared with ventilation imaging using Kr-81m. The initial deposition pattern and subsequent clearance characteristics of the aerosol provide a useful differentiation between the healthy and diseased lung. These differences are more obvious than those offered by the Kr-81m ventilation scan. Regional quantitation of the aerosol data reveals a finer detail that has diagnostic potential, and significant differences in aerosol deposition were measured between smokers and nonsmokers, in our healthy volunteer group, where no ventilation abnormalities were seen.

## APPENDIX

Calculation of radiation dose to the lungs following inhalation of 5 $\mu$m polystyrene particles labeled with 500 $\mu$Ci Tc-99m.

Radiation Dose (Emery and Fowler) $D = 2.13 \times c \times [\bar{E}_l + \bar{E}/\Delta I] \times t_E \times 1.44$ rads, where

$c$ = concentration ($\mu$Ci/g);
$\bar{E}_l$ = average energy/disintegration (MeV) for locally absorbed radiations (e.g. beta-rays, soft X-rays);
$\bar{E}I$ = average energy/disintegration (MeV) for gamma rays;
$\Delta I$ = absorbed fraction for gamma rays;
and
$t_E$ = effective half-life in hours.

The following assumptions are made in the calculations:

1. Approximate uniform distribution of tracer in the lungs.
2. Mass of lungs = 1 kg.
3. Absorbed fraction for Tc-99m gamma rays ($\Delta I$) = 0.14.
4. $\bar{E}_l$ = 0.014 MeV and $\bar{E}I$ = 0.126 MeV.
5. 30% of aerosol deposited (= 150 $\mu$Ci) cleared with biologic half-time of 3 hr. Hence $t_E$ = 2 hr.
6. 70% of aerosol deposited (= 350 $\mu$Ci) cleared with biologic half-time $\gg$ physical half-life of Tc-99m. Hence $t_E$ = 6 hr.

Therefore,

$$D = \frac{2.13}{1000} \times [(350)(6) + (150)(2)] \times [0.014 + (0.126)(0.14)] \times 1.44 \text{ rads}$$

$$= 2.13 \times 2400 \times 0.03164 \times 1.44 \text{ millirads}$$

$$= 233 \text{ millirads}$$

For a subject demonstrating no clearance,

$$D = 2.13 \times \frac{500}{1000} \times [0.014 + (0.126)(0.14)] \times 6 \times 1.44 \text{ rads}$$

$$= 291 \text{ millirads}$$

## FOOTNOTES

* Hammersmith MRC Cyclotron Unit, London
† Martindale Type A, London

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