Dr. Itoh: *Sometimes this occurs, but in COPD—3, mostly with pulmonary emphysema, patients can never cough up the hot spots.*

Dr. Newhouse: *That would suggest that they are not just blobs of secretion that have trapped radioactivity.*

Dr. Nadel: *It would be very interesting to look at the relationship between esophageal pressure and deposition. I would also predict that the effect of lung volume, particularly in patients who do not have very severe emphysema, would be very great on positive end-expiratory pressure—and would have a major effect on your observations. If you increased effort during exhalation, deposition during exhalation would increase as compression increased; if you used a flow-limiting segment outside the mouth to limit compression, you would predict that deposition during exhalation would decrease. These studies could sort out how important is the mechanism of expiratory deposition.*

The Characterization of Radioaerosol Deposition in the Healthy Lung by Histogram Distribution Analysis*

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Thirteen healthy nonsmoking volunteers inhaled an 8.1 μm (MMAD) radioaerosol on two occasions. Aerosol deposition pattern within the right lung, as recorded by a gamma camera, was expressed as the 3rd and 4th moments of the distribution histogram (skew and kurtosis) of radioactivity during the first ten minutes after aerosol inhalation. Deposition pattern was also expressed as the percentage of deposited activity retained within the lung at 24 hr (24 hr % retention) and found to be significantly correlated with measures of skew ($P < 0.001$). Tests of pulmonary function (FEV_1, FVC, and MMFR) were significantly correlated with skew. Correlations were also demonstrated for these pulmonary function tests with 24 hr % retention but at lower levels of significance. Results indicate that changes in measures of forced expiratory airflow in healthy human volunteers influence deposition pattern and that the skew of the distribution of inhaled radioactivity may provide an acceptable index of deposition pattern.

The last two decades have witnessed increased interest in the deposition and subsequent clearance of inhaled particles and their role in the pathogenesis of lung disease. The ability to define the penetration and pattern of deposition of inhaled particles is an essential prerequisite to the investigation of lung deposition and clearance. We have therefore derived quantitative indices of deposition pattern from two-dimensional images of radioaerosol deposition in the healthy human lung, compared results with the activity retained in the lung at 24 hours, and examined the relationship of such indices to tests of pulmonary function.

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Materials and Methods

Thirteen nonsmoking male and female subjects, aged 20 to 48 years, were studied twice, each having given informed consent. Tests of forced expiratory airflow (FEV_1, FEV_1/FVC%, and FEF25-75%) were made on each subject, the best of three results being recorded for each individual. Subjects inhaled an 8.1-μm (MMAD) Fe_2O_3 monodisperse aerosol (geometric SD of 1.1) tagged with ^{99m}Tc (half-life of six hours) and produced by a spinning disk generator. Aerosol was inhaled for three to five minutes with a breathing pattern of 16 breaths per minute, tidal volume (V_T) of 0.7 L, and average inspiratory flow ($\dot{V}$) of 0.5 L/sec. After inhalation the subjects were seated with their backs against a gamma camera (Pho-Gamma III gamma camera, Searle Co, Ltd). Deposited activity was recorded for the initial ten minutes and subsequently at 24 hours for one hour. Correction was made for background activity and isotope decay. Data recording, processing, and retrieval were performed with a Varian Varicam V72 computer.

An anteroposterior chest roentgenogram, with the seated subject breath-holding at functional residual capacity (FRC), was taken before each study. Anatomic dimensions of the lung edge were transferred from the roentgenogram of the right lung to a life-sized print of the gamma camera image. Coordinates derived from this print were transferred to the computer so that the boundary of the lung edge could be drawn on subsequent displays of the gamma camera image. The deposition image was made up of a matrix of 5-mm square picture elements (pixels). Histograms of the distribution of the number of pixels expressed as a percentage of the total number of pixels contained within the boundaries of the lung (ordinate) and the number of counts per pixel expressed as a percentage of the mean activity per pixel (abscissa) were constructed for each of the paired studies. Two examples of paired distribution histograms are shown in Figure 1. The histograms were then characterized in terms of the third and fourth moments of distribution (skew and kurtosis).

The formulas used in computing skew and kurtosis are as follows:

$$\text{Skew} = \frac{\sum^{N} (X - \bar{X})^3}{S_x^3 N} \qquad \text{Kurtosis} = \frac{\sum^{N} (X - \bar{X})^4}{S_x^4 N} - 3,$$

where N = total number of pixels, X = counts of activity per pixel, $\bar{X}$ = mean counts per pixel, and S_x = standard deviation of the histogram distribution.

Activity remaining within the lung 24 hours after aerosol inhalation was expressed as a percentage of the initial deposited activity. The 24-hour percent retention was considered to indicate the amount of activity deposited beyond the mucociliary escalator.

Results

Measures of skew and kurtosis uniquely describe each distribution histogram. Skew describes the asymmetry of the histogram so that the histograms for the paired

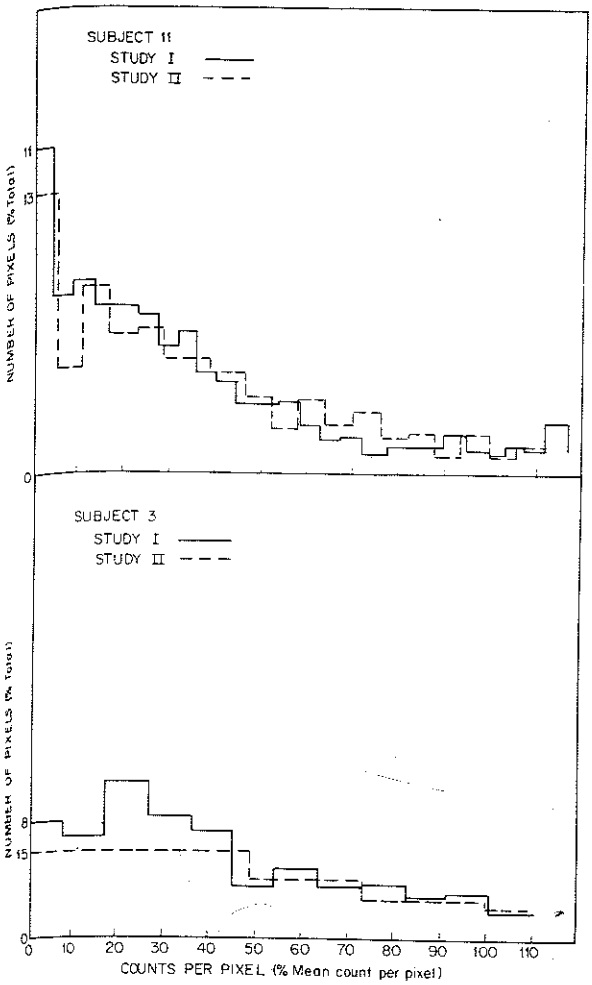

FIGURE 1. Two examples of paired deposition distribution histograms: study I, continuous line; study II, broken line. Common horizontal axis adjusted for mean count per pixel and vertical axis for both total number of pixels and mean count per pixel, facilitating the superimposition of paired histograms for each subject. For clarity scales on vertical axes are shown only where histogram intersects with axes. Such adjustments were not required for calculations of skew and kurtosis. Histogram distributions of subject 11 (*top*) yield high values of skew and kurtosis consistent with central deposition; of subject 3 (*bottom*) yield low values of skew and kurtosis consistent with peripheral deposition.

studies of subject 11 yielded high positive values of skew (2.7 and 3.2). Similarly, kurtosis, which describes the sharpness of the histograms, was also high for subject 11 (8.2 and 12.9). In contrast, values of skew (1.3 and 0.9) and kurtosis (1.9 and 0.6) were low for subject 3. Group mean values for skew were 2.3 ± 0.8, for kurtosis 6.8 ± 3.5, and for 24-hour percent retention 12.8 ± 8.6 (mean ± 1 SD).

Compared with measures of skew and kurtosis, 24-hour percent retention showed greater intra- and inter-subject variability. Both skew and kurtosis were inversely correlated with 24-hour percent retention ($P < 0.001$; Fig 2), indicating that high values of skew and kurtosis were compatible with central deposition and low values compatible with peripheral deposition.

Despite selecting healthy volunteers who were free

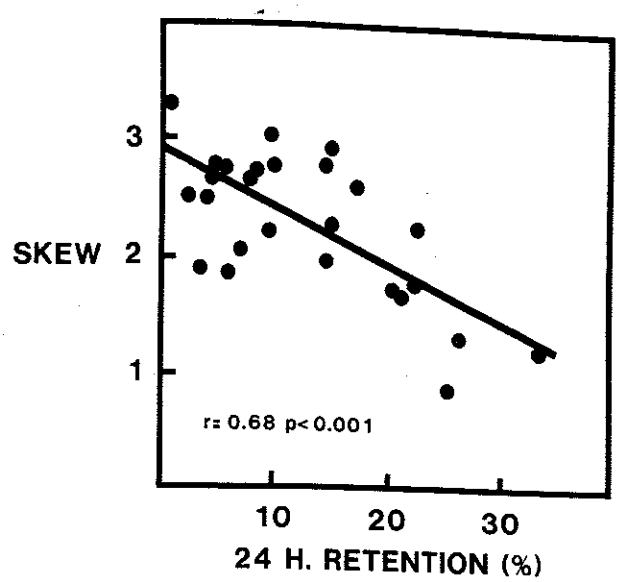

FIGURE 2. Regressions of skew against 24-hour percent retention for 13 paired studies in healthy subjects. Least squares regression line is shown. As values of skew increase (more central deposition), lower values of 24-hour percent retention are observed.

from cardiopulmonary symptoms, seven subjects showed evidence of mild airway obstruction (less than 80 percent of predicted values for tests of forced expiratory airflow). Regression analysis showed skew to be inversely correlated, with FEV_1 (percent predicted, $P < 0.01$), $FEV_1/FVC\%$, (percent predicted, $P < 0.05$), and FEF25-75%, (percent predicted, $P < 0.001$; Fig 3). Significant correlations of kurtosis with the same tests of pulmonary function were also obtained but at a slightly lower level of significance ($P < 0.01$, $P < 0.05$, and $P < 0.001$, respectively). However, the 24-hour percent retention was not significantly correlated with FEV_1 (percent predicted), and correlations with $FEV_1/$

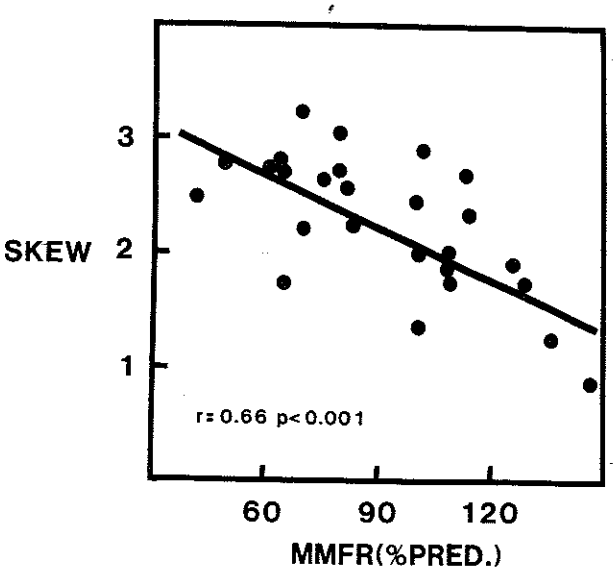

FIGURE 3. Regression of skew against FEF 25-75% (MMFR) (percent predicted) for 13 paired studies in healthy subjects. Least squares regression line is shown. With increasing airway obstruction (reduced MMFR), more central deposition of inhaled aerosol (increasing skew) is observed.

FVC (percent predicted) and FEF25-75% (percent predicted) only just reached significance at the $P < 0.05$ level.

Discussion

The penetration, deposition, and subsequent clearance of inhaled aerosol particles vary greatly depending on the particle size, breathing pattern, and the geometry of the conducting airways.[1-4] It has been necessary, therefore, to quantify aerosol deposition objectively in terms of the 24-hour percent retention or initial deposition indices.[5-9] Measurements of skew and kurtosis of the distribution of a deposited radioaerosol have several inherent advantages over the 24-hour percent retention as indices of deposition pattern. Once the lung boundary has been defined, skew and kurtosis can easily be calculated to provide dimensionless indices of deposition which are independent of lung size and the total amount of deposited aerosol. Although the 24-hour percent retention is widely used as a measure of deposition pattern, it relies on the assumption that it represents only aerosol deposited beyond the mucociliary escalator and that there is relatively little clearance from this part of the lung during the first 24 hours. In a recent animal study, detectable amounts of aerosol were retained in the trachea of rats 24 hours after deposition.[10] The 24-hour percent retention may therefore not provide an accurate measure of deposition pattern in investigations where predominantly central deposition is required and in which values of retained activity at 24 hours are therefore small. The significant correlation of skew and kurtosis with 24-hour percent retention ($P < 0.001$) would indicate that retained activity at 24 hours does indeed reflect the initial deposition pattern despite much greater intra- and intersubject variability. This greater variability of 24-hour percent retention, however, resulted in poorer correlations with the tests of forced expiratory airflow.

Variations in aerosol deposition have previously been related to the difference in airway function as defined by tests of forced expiratory airflow in patients with obstructive lung disease.[6-8,11,12] However, dependence of deposition pattern (as defined here in terms of skew and kurtosis) upon FEV_1, $FEV_1/FVC\%$, and FEF25-75% in healthy subjects has not been previously described.

Conceptually and practically, aerosol penetration appears to be better defined by indices derived from the initial deposition pattern than by measures of retained activity at 24 hours. The development and implementation of accurate and reproducible deposition indices is essential if meaningful comparisons of data from different investigators are to be made. The analysis of the distribution histogram of deposition in terms of skew and kurtosis appears to provide a simple and sensitive index of deposition pattern.

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Discussion

Dr. Swift: *The indices you have suggested are integral to the whole lung. I wonder if you have considered looking at indices of homogeneity which might take into account the relative pixel density in adjacent regions of the lung.*

Dr. Garrard: *The reason we used these indices is that all you need to do is define the lung edge for the gamma camera image. Thereafter, the computer will calculate skew and kurtosis very simply. All other measures we tried required careful definitions of regions of interest.*

Dr. Fazio: *All these indices treat the lung, a three-dimensional organ, as a bi-dimensional organ. Rotating gamma cameras can provide cross-sectional images of the lung. If you do this with a radioactive gas to give you the lung volume, and then with aerosol, you can work out a penetration index for each section of the lung.*

Dr. Garrard: *The approach we have presented is something that maybe many people could use; the algorithms for the computer are very simple.*

Dr. Gerrity: *Tomographic images would require relatively large amounts of activity to be inhaled in order to be statistically meaningful for quantitative analysis.*