Early Detection of Chronic Obstructive Pulmonary Disease Using Radionuclide Lung-Imaging Procedures*

George V. Taplin, M.D.;** Donald P. Tashkin, M.D.;† Sauvantara K. Chopra, M.D.;‡ Osvaldo E. Anselmi, M.D.§ Dennis Elam, M.S.;‖ Barry Calvoarse;‖ Anne Coulson,* Roger Detels, M.D.;§§ and Stanley N. Rokaw, M.D., F.C.C.P.; ||

One hundred subjects answered a respiratory questionnaire and underwent a physical examination, tests of pulmonary function, and three radionuclide lung-imaging procedures. The results of the radionuclide procedures were compared with each other and with pulmonary function tests and other diagnostic findings to determine their relative sensitivity for detecting evidence of early obstructive airway disease. Perfusion lung imaging was less sensitive than most of the other diagnostic tests evaluated. The aerosol and xenon lung-imaging procedures revealed abnormalities with approximately the same frequency as each other, but more often than any one group of pulmonary function tests, including spirometric data, maximal expiratory flow-volume curves, alveolararterial oxygen gradient, or indices derived from single-breath nitrogen washout. We concluded that xenon and aerosol lung-imaging studies are sensitive and useful screening procedures for detecting evidence of early localized obstructive airway disease and for locating regional abnormalities in the airways of patients with respiratory disease.

Lung-imaging procedures with inhalation of radioaerosol or radioactive $^{133}$Xenon gas have the capability of detecting abnormalities of airway patency and distribution of ventilation on a regional basis.1-3 In contrast, tests of pulmonary function do not reveal the site(s) of either partial or complete obstruction of the airways and may fail to detect any functional abnormality in the presence of known localized disease involving as much as 25 to 30 percent of the lung.8 Recently, we reported the findings in 70 subjects in whom conventional tests of pulmonary function were compared with radionuclide (mainly radioaerosol) lung-imaging procedures.3 The present study analyzes the results of lung-imaging studies, pulmonary function tests (including measures considered to be sensitive indicators of early obstructive abnormality), and other pulmonary diagnostic procedures in an additional 100 subjects and compares the findings from lung-imaging after inhalation of $^{133}$xenon with those from a modified radioaerosol examination in which lung images were obtained immediately and again one to two and four to six hours after inhalation of the aerosol. Aerosol lung imaging was repeated at these intervals in an effort to determine the validity of images obtained immediately after inhalation.

**MATERIALS AND METHODS**

Subjects were selected from residents of census tracts in Long Beach and Lancaster, Calif, who had undergone

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*From the Laboratory of Nuclear Medicine and Radiation Biology and the Departments of Radiological Sciences and Medicine, School of Medicine, and the School of Public Health, University of California, Los Angeles. Supported in part by the California Research and Medical Education Fund of the California Lung Association, by grant HR4-8013 from the National Heart and Lung Institute, by contract 84-(4-1) GEN-12 between the Energy Research and Development Agency and the University of California, and by grants-in-aid from the Radiopharmaceutical Division of Mallinckrodt Chemical Works and from E. R. Squibb and Sons.

**Professor of Nuclear Medicine and Radiological Sciences; Director, Nuclear Medicine Research Laboratory, Department of Radiological Sciences; and Associate Director, Laboratory of Nuclear Medicine and Radiation Biology.

†Adjunct Assistant Professor of Medicine and Fellow in Nuclear Medicine, Laboratory of Nuclear Medicine and Radiation Biology.

‡Visiting Scientist, Laboratory of Nuclear Medicine and Radiation Biology (from University Hospital, Porto Algre, Brazil).

‖Senior Staff Research Associate, Laboratory of Nuclear Medicine and Radiation Biology.

§Staff Research Associate, Pulmonary Disease Division, Department of Medicine.

§§Senior Statistician, School of Public Health.

‖Professor of Epidemiology, School of Public Health.

||Associate Clinical Professor of Medicine.

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Reprint requests: Dr. Taplin, Laboratory of Nuclear Medicine, 900 Veteran Avenue, Los Angeles 90024.

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screening studies of pulmonary function in a mobile laboratory. A 3-percent sample of the screened subjects was referred to the University of California, Los Angeles, for reevaluation. Approximately one-quarter of these subjects were randomly selected by choosing subjects studied at the mobile laboratory, and the remaining three-quarters were known to have some abnormality based on a respiratory questionnaire, spirometric data, or nitrogen-washout findings. Of the 100 subjects examined, there were 50 men and 50 women, ranging in age from 18 to 98 years, with an average age of 51 years.

**Pulmonary Function Testing**

After giving informed consent, each subject answered a detailed respiratory questionnaire and underwent a complete physical examination, spirometric determinations of forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and mean forced expiratory flow rate during the middle half of the FVC (FEF25-75%), and measurement of closing volume (CV) fraction using a modification of the technique of Anthonisen et al. The difference in nitrogen concentration between 750 and 1,250 ml of expired volume was also calculated from the single-breath nitrogen-washout curve. The methods of performing these pulmonary function tests and calculating their data are described in our initial report. In addition, closing capacity (CC) was calculated by adding residual volume (RV) determined by helium dilution to CV and expressing this sum as a percentage of total lung capacity. Other studies included measurements of maximal expiratory flow rates at 50 percent (Vmax50%) and at 25 percent (Vmax25%) of vital capacity above RV from the best of five maximal expiratory flow-volume curves and measurements of arterial pH, arterial carbon dioxide tension (PaCO2), and arterial oxygen pressure (PaO2) using standard electrodes. The alveolar-arterial oxygen pressure difference (P[A-a]O2) was calculated from the measured values of PaO2 and PaCO2, assuming a respiratory exchange ratio of 0.8.

**Lung-Imaging Procedures**

On the same day, each subject underwent radioaerosol, perfusion, and radioactive xenon (single-breath and washout) lung-imaging procedures before or after pulmonary function tests. The three radionuclide procedures were performed routinely. Only posterior lung images were obtained with 133Xenon, whereas perfusion imaging and aerosol imaging were performed in all four projections. Details of the techniques used for radionuclide lung imaging in our subjects were described previously.

Delayed aerosol lung images were obtained one to two hours after inhalation of the radioaerosol in 96 subjects again after four to six hours in 70 subjects, and on the next day (after 22 to 26 hours) in ten individuals. The repeated examinations were made to distinguish patterns of transiently excessive deposition in the major airways (possible false-positives) from those which remain abnormal for several hours (true positives).

During the present study, the ultrasonic aerosol generator was modified to operate at 2.9 MHz, rather than at 1.4 MHz, resulting in a reduction in the aerodynamic mass mean diameter of the aerosol droplets to less than 2.0 μm, as ascertained by retention in the pulmonary parenchyma at 24 hours of approximately 90 percent of the aerosol initially deposited in the respiratory tract.

**Interpretation of Conventional Procedures**

The respiratory questionnaire was judged to be abnormal if the subject fulfilled previously defined criteria for a definite abnormality in any of the following categories of symptoms: cough; production of sputum; increased cough and production of sputum; acute chest illnesses; wheezing; breathless-

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**Figure 1.** Top row, Radioaerosol lung images in standard four projections taken immediately after inhalation of nebulized 113m-indium colloid in normal 31-year-old man. Note uniform distribution throughout pulmonary fields and absence of deposition in stomach or airways. Bottom row, 133Xenon lung images in same subject and in same upright position taken during breath-holding, immediately after inhaling 10 millicuries of gas, and subsequently at 1 to 1.5, 2.0 to 2.5, and 3.0 to 3.5 minutes while breathing room air. Results of pulmonary function tests (FEV1, FEF25-75%, single-breath oxygen test, and PaO2) were normal.
Figure 2. Top row. Sequential radioaerosol (\(99m\)technetium sulfur colloid) lung images (posterior views) immediately after inhalation of test material and subsequently after 3, 5, and 22 hours in apparently normal 22-year-old man. Note mildly excessive deposition in major airways and stomach persisting for three hours but clearing by five hours and showing normal distribution at 22 hours. Bottom row. Xenon lung images during breath-holding appear normal, but there is evidence of air trapping or small airway obstruction at right base. Results of pulmonary function tests were normal, except for FEF25-75% (54 percent of predicted) and PaO\(_2\) (82 mm Hg).

Figure 3. Top row. Sequential radioaerosol (\(99m\)technetium sulfur colloid) lung images (posterior views) immediately after inhalation and again after 2.5, 4, and 22 hours. Note excessive deposition in trachea and major airways, with reduced penetration to periphery of lung laterally and at both bases in initial image. Similar abnormalities reappear after 2.5 and 4 hours, and there is uneven distribution at both bases in 22-hour image (56 year old man with chronic bronchitis). Bottom row. Normal distribution of xenon during breath-holding but evidence of air trapping at both bases in images taken during washout at 1.0 to 1.5, 2.0 to 2.5, and 5.0 to 5.5 minutes. Results of pulmonary function tests were moderately abnormal (FEV\(_1\), 64 percent of predicted; FEF25-75%, 53 percent of predicted; single-breath oxygen content, 2.41 L; and PaO\(_2\), 76 mm Hg).
ness; or a history of diagnosed respiratory illness. Smoking history was considered significant if the subject was currently smoking an average of at least one cigarette per day or had in the past smoked on the average at least one cigarette per day for at least one year. Findings from the examination of the chest were considered abnormal in the presence of any one or more of the following physical findings: rhonchi; rales; wheezes; localized dullness to percussion; poor diaphragmatic movement; generalized hyperresonance and diminished breath sounds; intercostal or supraclavicular retractions; deformities of the chest wall; or signs of cor pulmonale.

Spirometric indices (FVC, FEV₁, and FEF₂₅₋₇₅%) and the values for Vmax₅₀% and Vmax₂₅% were considered abnormal if they were more than 1.64 standard deviations below the predicted values derived from the regression equations of Morris et al⁹ and of Knudson et al¹⁰ respectively. Values for the change in nitrogen concentration exceeding 1.8 percent were considered abnormal.¹¹ Values for CV and CC were considered abnormal if they exceeded two standard deviations above the mean predicted values of Buist and Ross.¹² The values for P(A-a)O₂ were considered abnormal if they exceeded by two standard deviations the age-adjusted predicted values calculated from the data of Sorbini et al.¹³ The result of pulmonary function tests were classified as mildly abnormal (+) if the FEV₁ and FVC were normal but either FEF₂₅₋₇₅% or the results of one or more of the other tests of pulmonary function were abnormal; as moderately abnormal (+++) if the FEV₁ was abnormal but greater than 50 percent of the predicted value; and severely abnormal (++++) if the FEV₁ was less than 50 percent of the predicted value.

**Interpretation of Radionuclidic Lung Images**

The lung images were read independently by two authors (G.V.T. and S.K.C.) separately, without prior knowledge of the history, results of pulmonary function tests, or findings on chest x-ray films. In cases of disagreement, the final interpretation was based upon discussion and reevaluation of the images by three of the authors at a combined session. Agreement between the classification of images by the two interpreters as normal or abnormal was 88 percent.

**Aerosol Patterns.** Aerosol patterns were considered abnormal if the distribution was uneven, with discrete areas of increased and irregular regions of decreased radioactivity in the pulmonary parenchyma, or if there was excessive deposition in the regions of the major airways.² The aerosol pattern was classified as mildly abnormal (+) when there was slightly excessive deposition in the major airways or slightly uneven distribution involving less than 25 percent of the pulmonary parenchyma, or both. The images were considered moderately abnormal (+++) if there was either definitely excessive central deposition or distinctly uneven deposition in the smaller airways involving 25 to 50 percent of the lung. Aerosol images were considered severely abnormal (++++) when there were gross abnormalities of deposition in either the major or minor airways, together with absent or reduced deposition in more than half of the pulmonary parenchyma. Examples of normal and mildly, moderately and severely abnormal aerosol and xenon images are shown in Figures 1, 2, 3, and 4 respectively.

Abnormal aerosol patterns were further classified by division into those patterns showing excessive deposition in the major airways (central or type-A pattern) and those showing

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**Figure 4.** Top row, Initial anterior and posterior aerosol lung images and repeated images after 2 and 24 hours in 41-year-old man with severe bronchitic chronic obstructive pulmonary disease. Note grossly abnormal deposition in trachea and major airways and numerous small round "hot spots" in both mid-lung regions associated with little, if any, penetration to periphery of lung in initial aerosol images, with same pattern at 2 and 24 hours, except that at 24 hours, evidence of peripheral deposition became visible after major airways had partly cleared. Bottom row, Xenon lung images. Initial xenon image during breath-holding shows grossly reduced filling of more than half of lung and evidence of air trapping in right lung during washout. Results of pulmonary function tests were severely abnormal (FEV₁, 35 percent of predicted; FEF₂₅₋₇₅%, 9.4 percent of predicted; single-breath oxygen content, 3.21 L; and PaO₂, 61 mm Hg).

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both excessive central deposition plus discrete areas of relatively high radioactivity throughout the pulmonary par-enchyma (mixed or type-B pattern). Examples of these two types of aerosol patterns are shown in Figure 5.

**Perfusion images.** Perfusion images represent the distribution of pulmonary arterial blood flow and can localize lobar, segmental, or subsegmental areas of ischemia. These images were graded as mildly (+), moderately (++), or severely (+++) abnormal according to the visually estimated percentage of lung deprived of arterial blood flow, namely, less than 25 percent as mild, 25 to 50 percent as moderate, and more than 50 percent as severe impairment of the pulmonary arterial blood flow.

**Xenon Lung Images.** Xenon lung images were examined for uneven distribution of ventilation during breath-holding and for localized trapping of air, that is, regions becoming apparently more radioactive during washout. The latter abnormalities indicate the effects of partial airway obstruction or poorly ventilated emphysematous regions of the lung. These images were similarly graded as mildly (+), moderately (++), and severely (+++) abnormal if the visually estimated volume of poorly ventilated or nonventilated lung was, respectively, less than 25 percent, 25 to 50 percent, and more than 50 percent.

Xenon lung images were further classified by division into those patterns which showed normal distribution during breath-holding but abnormal images during washout (type-A xenon pattern) and those patterns which were abnormal during both breath-holding and washout (type-B xenon pattern). Examples of these two xenon patterns are shown in Figure 6.
Table 1—Interrelationships among Various Abnormal Findings in 100 Subjects

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<th>Variables</th>
<th>No. of Subjects*</th>
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<th>Symptoms</th>
<th>Physical Findings</th>
<th>Spirometric Data</th>
<th>Flow-Volume Loop</th>
<th>CV Curve</th>
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*Number of subjects equals total number of subjects with abnormal results for each variable listed at left side of table.

**Coprevalence of pairs of abnormalities (expressed as percentage), given that subjects have abnormal results for variable listed at left side of table.

#### RESULTS

The interrelationships among the numbers of subjects classified as abnormal on the basis of history, physical findings, pulmonary function tests, and radionuclide lung-imaging procedures in 100 subjects are presented in Table 1. Sixty percent of the subjects were cigarette smokers, and more than 50 percent of the total sample had definite symptoms of respiratory disease. Abnormal physical findings were found in less than 20 percent of the subjects. Abnormalities in any group of pulmonary function tests (spirometric data; flow-volume curve; CV, change in nitrogen concentration, and CC; or P[A-a]O₂) were observed in approximately 30 to 40 percent of the subjects, and abnormalities in aerosol and xenon lung imaging were noted in approximately 40 to 45 percent of the subjects. Of the 60 cigarette smokers and 53 subjects with symptoms of respiratory disease, roughly 25 percent had abnormalities on physical examination, 40 to 50 percent had abnormalities in the results of one or more of the pulmonary function tests, and 50 to 55 percent had abnormalities in xenon or aerosol lung imaging. Of the 17 subjects with physical findings suggestive of respiratory disease, 59 to 71 percent (10 to 12) had abnormalities on pulmonary function tests, whereas 77 to 88 percent (13-15) had abnormal radionuclide inhalation studies.

The comparisons of the degrees of abnormality shown with xenon, aerosol, and perfusion lung imaging and with pulmonary function tests were made. There was a fair to good correlation between the degree of abnormality on pulmonary function tests and that on xenon (r = 0.37) and aerosol (r = 0.59) lung imaging, respectively. The comparison of the degrees of abnormality shown by the three radionuclide lung imaging procedures is presented in Table 2. Of the 55 subjects with normal xenon

#### Table 2—Relationships of Degrees of Abnormalities among Radionuclide Lung-Imaging Procedures

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<th>Procedure</th>
<th>No. of Subjects*</th>
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</table>

*Number of subjects equals total number of subjects with degrees of abnormality for each procedure listed at left side of table.

**Coprevalence of degrees of abnormalities (expressed as percentage), given that subjects have degree of abnormality for each procedure listed at left side of table.
images, 11 percent (six) had abnormal aerosol images, whereas 17 percent (ten) of the 59 subjects with normal aerosol patterns had abnormal xenon images; however, almost all of the radioaerosol images that were abnormal in the face of normal xenon patterns were only mildly abnormal (+) and vice versa. Moreover, the degrees of abnormality shown by these two imaging procedures (aerosol and xenon) were highly correlated (r = 0.71). Abnormalities in perfusion lung imaging were very rare (4 percent, or two subjects) in the absence of abnormalities in xenon and aerosol examinations. Abnormalities in perfusion imaging were present in 38 to 57 percent of the subjects with mild (+) to moderate (+ +) abnormalities in xenon and aerosol examinations; however, abnormalities in perfusion were noted in all subjects with severe abnormalities (+ + +) in xenon and/or aerosol examinations.

An analysis of abnormal patterns of aerosol and xenon pulmonary distribution is presented in Table 3. Of the 41 subjects with abnormal aerosol patterns, 23 had excessive deposition in the major airways (type-A aerosol pattern), whereas 18 had a mixed or type-B aerosol pattern. Of the 45 subjects with abnormal xenon distribution during breath-holding or during washout (or both), 32 had normal patterns during breath-holding but abnormal images during the washout phase (type-A xenon pattern); the remaining 13 had abnormal patterns during both breath-holding and washout (type-B xenon pattern). Over three-quarters of the subjects with central or type-A aerosol distribution had type-A xenon imaging patterns, and a similarly large proportion of subjects with type-B aerosol images had mixed or type-B aerosol distribution, indicating good agreement between the aerosol and xenon imaging patterns in each type.

An analysis of initial and delayed (1 to 2 hours and 4 to 6 hours) aerosol lung images was made in 98 subjects. Fifty-five had normal patterns on initial examination. Of the 41 subjects with aerosol images that were abnormal on initial examination, the abnormalities persisted in 37 subjects on the delayed examinations as well. The four subjects in whom delayed imaging showed a reversion from an abnormal to a normal pattern all had only mildly abnormal patterns of central deposition on the initial examination.

**Discussion**

The slightly greater frequency of abnormalities in aerosol or xenon lung images than in any group of pulmonary function tests performed in our subjects (of whom approximately 50 percent were selected either randomly or on the basis of respiratory symptoms without spirometric abnormality) suggests that these radionuclide procedures may be more sensitive indicators of obstructive airway disease than conventional tests of pulmonary function, including flow rates at mid-lung and low-lung volumes, P(A-a)O₂, and the measures derived from single-breath nitrogen washout (change in nitrogen concentration, CV, and CC), which are considered to be particularly sensitive detectors of early obstructive abnormality.¹⁷⁻²⁰ The ability of the aerosol and xenon studies to identify abnormalities in some individuals with entirely normal findings on pulmonary function tests²¹ may be related to the unique ability of the radionuclide procedures to detect abnormalities of the airways and of ventilation on a regional basis. On the other hand, the finding of the results of one or another of the pulmonary function tests to be abnormal in some subjects in whom aerosol or xenon imaging was normal suggests that the conventional and radionuclide procedures are complementary with respect to the detection of early obstructive disease. The ability of pulmonary function tests to disclose abnormalities in subjects

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**Table 3—Comparison of Abnormal Aerosol and Xenon Lung Images**

<table>
<thead>
<tr>
<th>Procedure and Pattern</th>
<th>No. of Subjects*</th>
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<tr>
<td>Type B</td>
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</table>

*Number of subjects with abnormal type or pattern of aerosol or xenon images listed at left side of table.

**Coprevalence of type and pattern of aerosol and xenon abnormalities (expressed as percentage), given that subjects have type or pattern of abnormality listed at left side of table.

†Type-A xenon pattern showed normal image during breath-holding and abnormal image during washout. Type-B xenon pattern showed abnormal image during both breath-holding and washout.
with normal aerosol and xenon images may be due, at least in part, to the fact that the pulmonary function tests are quantitative indices of overall function, whereas the radionuclide tests employed in this study were only qualitative, or at best semiquantitative measures of regional pulmonary function. It is very likely that the sensitivity of the radioactive xenon studies could be enhanced by measuring regional washout rates from different zones of each lung and that the sensitivity of the radioaerosol examinations might also be increased by quantitating relative amounts of deposition of the aerosol in different regions of the lung or by measuring rates of clearance of centrally deposited particles.

In our initial report, comparison of aerosol and xenon lung imaging suggested that the two radionuclide procedures were equally sensitive with respect to detecting abnormalities in subjects with and without other evidence of chronic obstructive pulmonary disease; however, only 22 of 70 subjects were examined with the xenon method. In the present study, both xenon imaging and aerosol imaging were performed in all 100 subjects. The xenon images were occasionally found to be abnormal in some respect when aerosol studies were normal and vice versa, or a disparity was noted in the degree of abnormality between the two procedures; however, the correlation between the xenon and aerosol techniques among all subjects was good (r = 0.71). These findings suggest that the two radionuclide inhalation procedures may give different, but complementary, information that the two techniques provide greater diagnostic assistance than either alone.

A central pattern of aerosol deposition (type-A aerosol pattern) showed a close association with abnormal xenon images found during the washout phase but not on the single-breath maneuver (type-A xenon pattern). These types of aerosol and xenon patterns were found most frequently in subjects with mild chronic obstructive pulmonary disease and no detectable or only mild abnormality on conventional pulmonary function tests. Such subjects might have slight irregularities in the large airways, resulting in abnormal deposition of aerosol, most likely as a result of increased turbulence and gravitational impaction. Previous studies by others have suggested that the small airways are the sites of early abnormality in patients with mild chronic obstructive pulmonary disease. Our findings on aerosol lung imaging suggest that these same individuals may also have mild abnormalities in the large airways which are not of sufficient magnitude to reduce spirometric flow rates. In addition, it appears that the xenon washout technique is more sensitive in detecting abnormalities in the small airways than physiologic measurements of the distribution of ventilation, such as the change in nitrogen concentration and the F(A-a)O2, probably because it detects abnormalities on a regional basis.

A mixed pattern of aerosol deposition (type-B aerosol pattern) was associated with abnormal xenon images found during both the breath-holding and the washout phases (type-B xenon pattern). These type-B patterns were generally observed in heavy smokers with symptoms of chronic bronchitis and moderate to severe abnormalities of pulmonary function. Such individuals may have more narrowing of both medium-sized and large airways, resulting in grossly uneven ventilation. Consequently, one would expect to find abnormal aerosol deposition in both the major and minor airways due to inertial impaction, as well as uneven distribution of xenon gas on the single-breath maneuver.

A more comprehensive analysis of possible false-positive initial aerosol images was made in the present study, in which 96 of 100 subjects received delayed examinations. Central aerosol deposition may be caused by excessively large particles (>5.0μm) or by abnormally rapid or shallow breathing patterns, or by both factors. These two variables were minimized in the present study by using small particles (2.0μm or less), by giving the patient a three-minute practice session of breathing an aerosol of 0.9 percent saline solution, and by directing the patient to breathe with a tidal volume of approximately 500 ml at a normal rate of 12 to 16 times per minute. Only 10 percent of the subjects having excessive central deposition initially showed normal images one to two hours later, as compared with 16 percent in our previous study. The lower frequency of possible false-positive patterns in the present study is most likely related to the use of a smaller-sized aerosol. Although some doubt remains regarding the significance of only slightly excessive central deposition in the image made immediately following radioaerosol inhalation, initial aerosol patterns classified as moderately or severely abnormal are nearly always indicative of obstructive airway disease. Longitudinal studies incorporating radionuclide inhalation procedures would be required to determine the specificity of isolated abnormalities detected by lung imaging but not by conventional pulmonary function tests or other routine diagnostic measures.

It is concluded that xenon and aerosol lung-imaging procedures are useful tools for detecting and localizing early obstructive airway disease and for confirming abnormalities found by conventional pulmonary function tests. Because the xenon single-
breath and washout procedure is equally sensitive but less time-consuming and complicated than initial and delayed aerosol imaging, xenon imaging is considered more feasible for possible use in future studies to assess the utility, sensitivity, and specificity of different diagnostic procedures in screening populations for early obstructive airway disease.

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