INVESTIGATIVE NUCLEAR MEDICINE

Lung Clearance Mechanisms in Obstructive Airways Disease

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Using radioaerosol inhalation lung cinescintigraphy, pulmonary clearance mechanisms were studied in 21 patients with obstructive airways disease. In none of them did we find homogeneous deposition of inhaled radioaerosol in the lungs, or a steady, constant, axial, and cephalad transport of radioactivity in the major airways. Of the 21 patients, 14 showed temporary but frequent stopping and starting of radioactivity in the airways in the course of lung clearance; in ten there was reversal of flow; in five migration of radioactivity from one bronchus into the opposite, bypassing the trachea and often followed by shuttling between right and left bronchi; and in four there was spiral or zigzag transport of radioactivity. The overall lung retention ratio in the first 2 hr was not abnormal, but the airway deposition ratio was significantly above normal, and airway clearance efficiency was below. The alveolar deposition ratio was also significantly smaller in these patients.

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In previous communications we have shown that "radioaerosol inhalation lung cinescintigraphy" is useful in dynamically demonstrating clearance mechanisms in the lungs (*1–4*). This potentially important nonrespiratory pulmonary function can be evaluated visually and quantitatively by this new modality of lung imaging.

Radioaerosol inhalation lung cinescintigraphy has shown that in normal subjects the transport of inhaled radioactive aerosol deposited in the airways is always axial and cephalad in direction, and steady in its motion. However, in smoking normal subjects a temporary stopping of clusters of radioactivity was often seen in the main bronchi, the carina and/or in the trachea (*2–4*).

In addition to visual evaluation of clearance mechanisms of the lung, we have introduced five indices to evaluate quantitatively the clearance of inhaled aerosol from the lungs. These are: (a) overall or regional lung retention ratio; (b) airway deposition ratio, (c) airway retention ratio, (d) airway clearance efficiency, and (e) alveolar deposition ratio (*4*). In normal subjects the overall and/or regional lung retention ratio appeared smaller in smokers than in nonsmokers, whereas the airway deposition ratio was greater in smokers. The airway retention ratio and airway clearance efficiency did not differ between the two groups, indicating that mucociliary clearance mechanisms are well maintained in normal subjects notwithstanding the smoking status. Because our cinescintigrams can reveal actual mucus clearance visually, and our knowledge of mucus transport mechanisms in obstructive airways disease is limited, we have applied this technique to a study of lung clearance mechanisms and their derangement in patients with obstructive airways disease (OAD).

MATERIALS AND METHODS

There were 21 patients in this group studied. They had no radiologically manifest parenchymal consolidation, fibrosis, or lung tumor. Acute symptoms such as frequent cough, massive sputum production, or temperature elevation were subsiding and the patients were clinically stable, requiring no oxygen. The diagnosis of obstructive airways disease was based on the criteria proposed by American Thoracic Society (*5*). There were 17 men and four women, age range 43 to 81, average 63. They were

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TABLE 1. LUNG FUNCTION DATA

Patient No.	Age	Sex	FVC* (ml)	%Pred.† (%)	$FEV_{1.0}$%‡R(%)	MMF§ (l/sec)	RV¶/TLC** (%)
1	81	M	1605	56	35	0.22	67
2	76	M	2491	85	60	0.99	46
3	71	F	1657	74	31	0.17	70
4	43	M	3159	85	27	0.40	48
5	64	M	2990	89	46	0.47	44
6	66	M	2500	78	30	0.22	59
7	61	M	3926	90	50	0.92	43
8	63	F	2081	81	24	0.15	58
9	74	M	2182	75	32	0.26	60
10	71	M	1732	60	17	0.13	74
11	70	M	2561	75	34	0.30	46
12	50	M	2072	58	21	0.18	70
13	52	M	1487	47	26	0.13	65
14	71	F	1780	88	70	0.95	—
15	67	M	1322	40	33	0.58	57
16	63	M	2533	78	37	0.39	49
17	61	F	1594	55	59	0.49	42
18	72	M	2294	74	50	0.68	56
19††	49	M	4775	131	76	2.79	33
20††	56	M	3739	101	85	5.10	22
21††	53	M	4187	114	61	1.88	35

* FVC: Forced vital capacity.
† %Pred: Percent of the predicted normal value (46).
‡ $FEV_{1.0}$%: Forced expiratory volume in one second/forced vital capacity.
§ MMF: Maximum mid-expiratory flow rate.
¶ RV: Residual volume.
** TLC: Total lung capacity.
†† Bronchial asthma during remissions.

all current or ex-smokers. The data on lung function tests are shown in Table 1. For those who were studied more than twice (Nos. 1, 2, 3, 9, 11), the lung function data for only the first study are shown, because there was little change in the subsequent studies. Chest radiography and perfusion lung imaging were done within a week of radioaerosol inhalation lung cinescintigraphy. Three patients with bronchial asthma (Nos. 19, 20, and 21) were studied during remissions.

The methods of acquiring the radioaerosol data and their analysis were the same as previously reported except that of 24 hr—the counting time was 10 min instead of 15 (*4*).

In brief, the deposition and movement of Tc-99m albumin aerosol was monitored continuously for 2 hr, starting immediately after the inhalation. The patient was comfortably supine on a bed in a dimly lit room, provided with background music, with a gamma camera viewing the chest from in front. The aerosol was ultrasonically generated and its median diameter was 3.73 μm with geometric standard deviation of 1.73 (*6*). In nine of the 21 patients, measurement of residual radioactivity was repeated for 10 min 24 hr later, with the patient in the same supine position. The data were stored in a computer in frame mode with a 64 × 64 matrix, each frame covering 10 sec. In five patients the initial 2-hr measurements were repeated from two to four times each 3 mo up to 2 yr. Thus 29 2-hr measurements were made in the 21 patients. Coughs, if any, were not specifically suppressed during the measurement.

The data stored were retrieved and ultilized in two ways: one editing the 720 10-sec frames into the cinematographic display (*1–4*), and the other used to calculate the five quantitative indices (*4*). Corrections were applied for physical decay. Indices (b) to (e) were calculated for the nine patients who were repeatedly studied at 24 hr. In calculating the five indices, radioactivity in the extrapulmonary airways was not taken into consideration because it is masked by radioactivity in the esophagus (*4*).

Student's t-test was used for statistical analysis (*7*). A p value of 0.05 or less was considered significant. Curve-fitting techniques were applied to all the data pairs and coefficients of determination, r^2, and regression

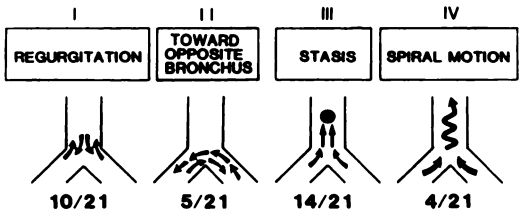

FIG. 1. Diagram of mucociliary transport patterns in obstructive airways disease. Numbers indicate frequency.

coefficients were calculated for four different regression functions; $y = a + bx$, $y = ae^{bx}$, $y = a + b \ln x$ and $y = ax^b$. When r^2 was the greatest for a particular regression function, that function was considered the best fit for the data pairs.

RESULTS

Radioaerosol inhalation lung cinescintigraphy. All 21 patients showed nonhomogeneous aerosol deposition patterns in the lungs (*9*) and the migration of radioactivity over the trachea and the major bronchi was extremely protean in its direction and transportation patterns. The abnormal mucus transport patterns were not appreciable from conventional spot images of the lung following radioaerosol inhalation as formerly obtained (*8*,*9*). Four abnormal transport patterns are diagrammed in Fig. 1.

Of the 21 patients, 14 showed a temporary but frequent stasis of radioactivity in the trachea or the major bronchi (Fig. 1). Even after radioactivity began to migrate up the trachea, it tended to stop on the way. Thus stopping and renewed migration were repeated many times. Migration was sometimes accelerated by coughing and clearing the throat, with the radioactivity finally swallowed or expectorated. In one of the 14 patients, cough appeared to be the major means of upward propulsion.

In ten of the 21 patients, reversal of the cephalad flow was seen along the path on the trachea of bronchi (Fig. 1). In two patients there was even regurgitation into bronchi where there was little initial deposition.

In five of the 21 patients, material was seen to pass across the carina from one main bronchus into the opposite one, rather than up the trachea (Fig. 1). In two of the five, shuttle movements of radioactivity between right and left bronchi were observed. An example is shown in Fig. 2, top, bottom. The patient was a 70-yr-old male (No. 11) with pulmonary emphysema and a history of recurrent infections. As shown in Fig. 2, top, a collection of radioactivity began to migrate from the right bronchus into the left, followed by shuttle movements between right and left bronchi. There was also an arrest of radioactivity in the trachea. As shown in Fig. 2, bottom, cough occurred at 97 min; radioactivity was pushed upward through the larynx, and some was swallowed into

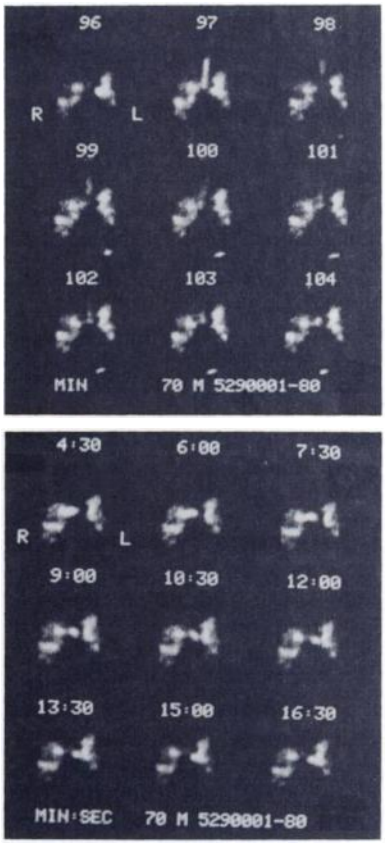

FIG. 2. Top: One-min images, starting from indicated times after radioaerosol inhalation (earlier phase), in 70-yr-old man with pulmonary emphysema and history of recurrent infections. Note shot of radioactivity gradually migrating from right bronchus into left. (Right lung is toward viewer's left.) Below left lung is swallowed radioactivity in stomach. Here image color code was normalized to peak activity detected. In actual radioaerosol inhalation lung cinescintigraphy, each 10-sec frame is transformed to cine mode to allow visual evaluation of dynamic mucus transportation and lung clearance. Bottom: Still images (later phase) from same patient. Cough occurred at 97 min, and radioactivity was pushed cephalad. At 98 min some radioactivity was swallowed into stomach where radioactivity again increased. Shuttle motions of radioactivity persisted between right and left bronchi after coughing subsided.

the stomach. Shuttle transport persisted between the right and left lungs after coughing. In all five of this group, cough finally propelled the aberrant radioactivity from the bronchi upward into the trachea.

Spiral or zigzag motions were seen during the upward migration of radioactivity in the trachea in four of the 21 patients: radioactive clusters took winding paths through the trachea instead of taking the usual axial course (Fig. 1).

Repeat studies were done in five patients anywhere from twice to four times every 3 mo or up to 2 yr apart. These showed few recognizable changes from the previous studies either in aerosol distribution or in radioactive migration patterns in the trachea. For example in Patient 9, zigzag motion was seen in all three studies, and in Patient 11 (Fig. 2, top, 2, bottom) the movement of

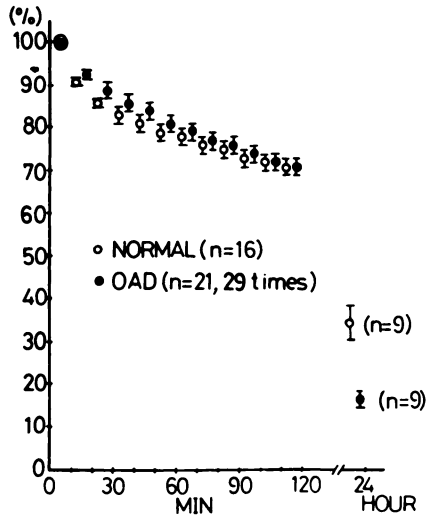

FIG. 3. Time course of overall lung retention ratio. For 2 hr there was no statistical difference between normals and patients with obstructive airways disease (OAD), but note difference in ratio at 24 hr.

radioactivity from the right bronchus into the left, followed by shuttle motion, was seen in two studies done 1 yr apart.

Quantitative analyses. *Overall lung retention ratio.* This ratio is the percentage of radioactivity in the lungs at each 10-min period when the total radioactivity during the initial 10 min is assumed to be 100%. Overall lung retention ratio was calculated from 29 measurements in 21 patients, and is shown in Fig. 3, where the data from the 16 normal subjects reported previously (*4*) are also shown for comparison. The normal subjects were not age-matched with the patient population.

The overall lung retention ratio was not different from that in the normal subjects during the initial 120 min. For this period, curve-fitting analysis indicated that in normal subjects the time course of the ratio is best expressed by $y = 116.6 - 9.2 \ln x$, where y is the ratio (%)

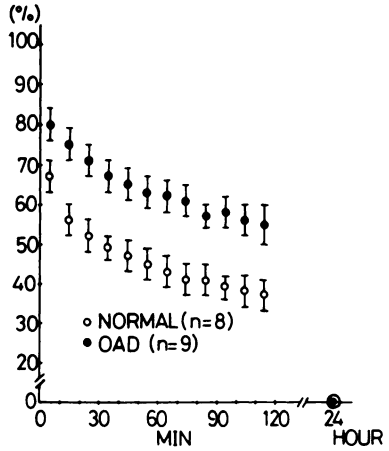

FIG. 4. Airway deposition ratio. Significant difference between normals and patients with obstructive airways disease (OAD) (0.005 < p < 0.05).

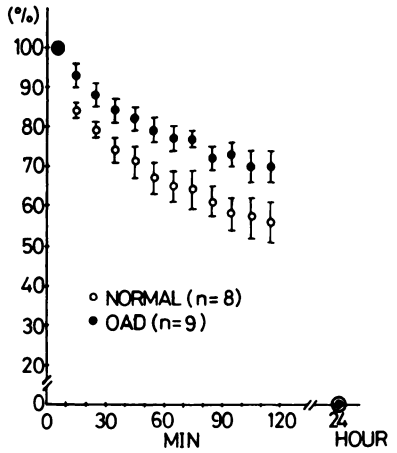

FIG. 5. Airway retention ratio. Significant difference between normals and patients with obstructive airways disease (OAD) (0.01 < p < 0.05).

and x is the time in minutes. For the patients with obstructive airways disease, the equation is essentially the same: $y = 117.6 - 9.3 \ln x$. The r^2 values were 0.995 and 0.972, respectively. At 24 hr, however, the overall lung retention ratio was significantly higher in the normals than in the patients ($p < 0.005$). This ratio at 24 hr is the same as the alveolar deposition ratio (see later).

Airway deposition ratio. This ratio is equivalent to overall lung retention ratio minus alveolar deposition ratio. It represents the fraction of radioactivity remaining in the ciliated airways at each time interval.

Figure 4 shows a clear difference in the airway deposition ratio between patients with obstructive airways disease and normal subjects ($0.005 < p < 0.05$). Curve-fitting for the initial 120 min indicated that for the patients with obstructive airways disease (OAD), $y = 96.0 - 8.3 \ln x$ fitted best, whereas for the normals, $y = 82.2 - 9.4 \ln x$ fitted best with r^2 values 0.967 and 0.997, respectively. In the patients with OAD, proportion of activity deposited in the ciliated airways was always greater than normal.

Airway retention ratio and airway clearance efficiency. The former indicates the percentage of the radioactivity initially deposited in the ciliated airways that

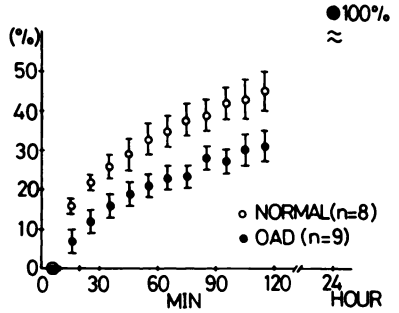

FIG. 6. Airway clearance efficiency. Significant difference between normals and patients with obstructive airways disease (OAD) (0.01 < p < 0.05).

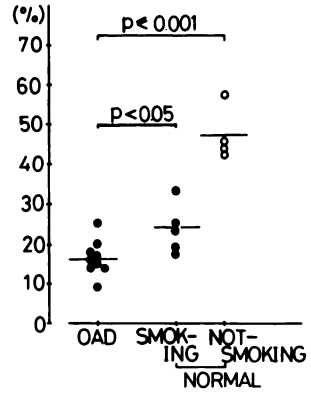

FIG. 7. Alveolar deposition ratio. Difference is statistically significant ($p < 0.005$) between normal group (smoking and nonsmoking) and patients with obstructive airways disease. Note also significant differences between OAD patients and normal subjects ($p < 0.05$) and nonsmoking normals ($p < 0.001$).

still remains there at each 10 min period. It normalizes the airway deposition ratio at 100% at the initial 10 min period. Airway clearance efficiency is equivalent, in percentage, to (100—airway retention ratio). These two indices were, respectively, greater and smaller than normal in the patients with obstructive airways disease (OAD) ($0.01 < p < 0.05$). Curve-fitting for the first 2 hr gave the following relationships: for the airway retention ratio, $y = 123 - 14.0 \ln x$, $r^2 = 0.995$ in normal subjects, and $y = 118.9 - 10.1 \ln x$, $r^2 = 0.973$ in the OAD patients (Fig. 5); for the airway clearance efficiency, $y = -23.2 + 14.1 \ln x$, $r^2 = 0.996$ in normals, and $y = -19.0 + 10.2 \ln x$, $r^2 = 0.972$ in the patients (Fig. 6).

Alveolar deposition ratio. This is the radioactivity remaining in the lungs at 24 hr, as a percentage of the initial total radioactivity there immediately after radioaerosol inhalation. It is equivalent to overall lung retention ratio at 24 hr. As shown in Fig. 7, the OAD patients showed a significantly smaller mean alveolar deposition ratio than the normal subjects.

Radioaerosol deposition patterns and perfusion lung images. All patients showed nonhomogeneous aerosol distribution patterns in the lungs (*9*), but the patients with bronchial asthma during remissions showed less variability. According to the classification previously reported (*9*), 13 of these patients tended toward a more central deposition, two toward a purely peripheral pattern, and one with central and peripheral intensities equal. In five patients repeated studies showed the deposition pattern repeating consistently.

Perfusion lung imaging also showed nonhomogeneous perfusion distribution in all the 21 patients studied. Again less variability was seen in patients with bronchial asthma during remissions. Patient 8 showed nearly absent perfusion in the entire right lung. In the regions where perfusion distribution was decreased or absent, aerosol deposition tended to be decreased or nearly absent.

DISCUSSION

In the normal human subjects or normal dogs, inhaled radioactive droplets landing in the ciliated airways are transported through the bronchi and trachea in a cephalad and axial direction, as reported previously (*1–4,10*). In our OAD patients, however, the transportation patterns were highly variable, and the clearances also differed greatly from normal. The abnormal patterns diagrammed in Fig. 1 occurred in the patients, and stasis was also seen, though of lesser degree, in the "normal" smokers (*4*). These dynamic aspects of deranged mucus transport in the airways have never been visually appreciated in vivo in man, whether by static sequential imaging following aerosol inhalation (*8,9*), or by measuring clearance of inhaled radioactivity (*11–15*), or by morphological studies of the cilia (*16*). One of the greatest advantages of "radioaerosol inhalation lung cinescintigraphy" is that these clearance mechanisms are vividly presented to the viewer, and the underlying serial data can also be used for quantitative analysis of overall or regional lung clearance mechanisms (*4*). We assume that our lung cinescintigram mirrors actual mucus transport; the question is why such aberrant phenomena occur in obstructive airways disease.

Mucociliary clearance and coughing are two main mechanisms of lung clearance (*17–20*). When mucociliary clearance of the lungs is discussed, we must consider it from at least two aspects: the mucus itself, and the cilia or ciliary coordination.

Inhaled particulate material is trapped on the outer mucus layer in the airways and transported toward the oropharynx by the underyling cilia (*21–23*). The role of mucus in the mucociliary clearance mechanism is vital, since it possesses specific rheological properties necessary for transport; particles cannot be cleared in its absence (*24,25*). Because excessive sputum production was not a problem in our patients, we did not pursue this aspect of mucus or its rheological characteristics in this study.

As is well known, the motion of adjacent cilia on an individual cell, or the motion among cilia of adjacent cells, is metachronally coordinated (*26,27*). One of the reasons why mucociliary transport in normal subjects is steadily cephalad toward the oropharynx is because of coordination of the adjacent cilia. The direction of the effective ciliary beat is considered to be in the direction of the doublets termed 5 and 6 (*28*), and to the direction of the basal feet (*29*). Congenitally malfunctioning cilia with variable direction of ciliary beat are characteristics of the immotile-cilia syndrome (*29–32*), but if microtubular changes could also be acquired (*33–36*), a state of ciliary disorder or incoordination of ciliary beats

on the surface could well be expected. We suspect that what we have observed in patients with obstructive airways disease could well be due to incoordinated ciliary beats; the various types of abnormal mucus transport pattern described here might result from this incoordination.

Whether the mucociliary clearance system in OAD is damaged or not has been studied extensively by various investigators (*12,17–20,22,37–42*). Mossberg thinks that impairment of mucociliary transport precedes the possible development of OAD in chronic bronchitis (*43*). There are reports, however, that clearance is even increased (*39*) or normal (*41*). The fact that deposition of inhaled particles is more centrally located on the ciliated airways in OAD, and that alveolar deposition ratio was not considered in interpreting the data, may have been a reason for reaching such conclusions.

In the present study, too, the overall lung retention ratio alone did not necessarily discriminate the patients with OAD from the normal subjects. Why is this so? We believe that in the patients with OAD the fraction of aerosol deposited in the ciliated airways is greater than that in the normal subjects. As evidenced in Fig. 4, this fraction at any time during the first 2 hr is also above normal in OAD (Fig. 5), indicating that mucociliary clearance is less efficient in OAD patients (Fig. 6). The alveolar deposition ratio (the fraction of inhaled aerosol deposited in the alveolar space) is naturally well below normal in OAD. Now overall lung retention ratio is the amount of radioactivity on the ciliated airways plus in the alveolar space at a particular time, divided by the initial total intrapulmonary radioactivity. Although mean lung retention ratios appeared incidentally to be similar between our OAD patients and the normals during the first 2 hr, they are expected to show different clearance patterns after 2 hr: in the normal subjects the overall retention ratio is expected to reach a plateau equivalent to alveolar deposition much earlier than in the OAD patients. In the latter, a plateau may or may not have been reached by 24 hr because of inefficient clearance from the ciliated airways. Actually we could often see some radioactivity remaining in the extrapulmonary airways even at 24 hr. Although in the present study we have conveniently defined that the radioactivity remaining in the lungs at 24 hr as equivalent to that in the alveolar space, or at least in the nonciliated distal airways where mucociliary clearance is not operative (*4*), whether this definition (*14,42,44*) is justified or not is open to question.

At any rate, overall lung retention ratio itself was not discriminative, but the other four indices clearly demonstrated on a quantitative basis that clearance mechanisms were less efficient in patients with OAD.

In 1972, Iravani and van As described the patterns of mucus transport in the entire tracheobronchial trees of normal and bronchitic rats, which they studied with a stereoscopic microscope. In the normal rats, all types of mucus particles, droplets, flakes, and plaques were transported towards the trachea. Although the direction of the effective stroke of ciliary beat was frequently divergent in adjacent fields, it was never directed caudally (*22*). In normal human subjects, too, the direction of the mucus flow, as elicited by our cinescintigrams, has never been directed caudally (*1–4*). In the bronchitic rats' bronchi, two main abnormalities of mucociliary function were observed. First, inactive zones were seen, in which no mucus transport or ciliary activity could be observed focally. The areas varied considerably in size and in the small zones of ciliary inactivity did not impair mucus transport (*22*). This finding seems exactly analogous to what we have observed in normal smokers (*2–4*) and more markedly in patients with OAD. The other abnormality was active ciliated cells or cell groups with altered functions: (a) reversal of the effective stroke of the ciliary beat, (b) the loss of the coordinated metachronism among cilia, and (c) altered types of the ciliary beat (*22*). Ciliary beat frequency itself in biopsy samples does not show any disease-specific difference (*36*). The dynamic changes in mucociliary transport observed in vitro in bronchitic rats' tracheobronchial trees seem to be actually taking place to various degrees in human subjects with obstructive airways disease. In this sense the work of Iravani and van As in bronchitic rats offers substantial support to our cinescintigraphic findings in human patients in vivo.

Although the real cause of the deranged mucociliary transport in OAD is not known, ciliary incoordination, a diminished number of cilia, abnormal rheological properties of the mucus, or the quantities of mucus produced may be intricately involved. At any rate, these aberrant mucociliary clearance mechanisms may contribute to the higher incidence of recurrent infections in patients with OAD.

Regarding the role of coughing and/or clearing of the throat in lung clearance, other authors found that in patients with chronic bronchitis who could not avoid coughing during the measurements, the amount cleared during 2 hr did not differ from that of healthy persons (*17–20*). In one of our patients (No. 13) the main clearance mechanism seemed to be related to coughs, but in the others any coughing or hawking appeared helpful only in initiating mucus migration or in temporarily accelerating mucus transport, often to be followed by arrest or back-flow. In this sense coughs and/or hawks are undoubtedly important clearance mechanisms, particularly proximally, but the mucociliary clearance mechanism seems to play a far more important role than coughs and/or hawks in lung clearance.

Since the tracheal mucociliary transport rate has been shown to correlate with lung mucociliary clearance in healthy subjects (*45,46*), one reasonable way to evaluate

lung clearance mechanisms in man would be to look at "radioaerosol inhalation lung cinescintigraphy" first, to get an idea regarding what is happening in the ciliated airways. Then, by calculating these five indices, we believe we can obtain a better idea of lung clearance on a quantitative basis as well.

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