

## INVESTIGATIVE NUCLEAR MEDICINE

## A Model for Assessing Bronchial Mucus Transport

J. E. Agnew, J. R. M. Bateman,\* D. Pavia, and S. W. Clarke

*Departments of Medical Physics and Thoracic Medicine, Royal Free Hospital and School of Medicine, London NW3*

**We propose a scheme for the assessment of regional mucus transport using inhaled Tc-99m aerosol particles and quantitative analysis of serial gamma-camera images. The model treats input to inner and intermediate lung regions as the total of initial deposition there plus subsequent transport into these regions from more peripheral airways. It allows for interregional differences in the proportion of particles deposited on the mucus-bearing conducting airways, and does not require a gamma image 24 hr after particle inhalation. Instead, distribution of particles reaching the respiratory bronchioles or alveoli is determined from a Kr-81m ventilation image, while the total amount of such deposition is obtained from 24-hr Tc-99m retention measured with a sensitive counter system. The model is applicable to transport by mucociliary action or by cough, and has been tested in ten normal and ten asthmatic subjects.**

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Clearance of mucus from the conducting airways of the lungs is a vital defense mechanism, and one that can be studied with inhaled insoluble radioactive particles. Small enough particles and slow inhalation make it possible to place particles on the whole bronchial tree from the main bronchi to the terminal bronchioles (1). Movement of the particles then reflects movement of the airways mucus on which they are deposited. Deposition over the whole bronchial tree, however, unavoidably implies a considerable spillover of deposition into the respiratory bronchioles and alveoli. Deposition in these sites is conveniently termed "alveolar deposition" and is often estimated from the proportion of particles remaining in the lung after 24 hr. The rationale for this is that clearance from the ciliated conducting airways takes less than 24 hr in normal subjects, whereas clearance from the alveoli is so slow that it may be dismissed as negligible over any 24-hr period. Thus, in any lung region seen by the gamma camera, the particles acting as a

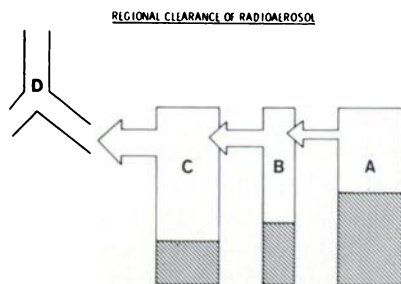
tracer for mucus transport have to be detected against a "background" of alveolar deposition. This background will be highest for peripheral zones and lowest for perihilar zones because of the differing volumes of conducting airways and of alveoli at these sites. Although gamma-camera measurement of regional retention at 24 hr is technically feasible even with a short-lived nuclide such as Tc-99m (2,3), it requires higher initial activity than is desirable in subjects undergoing multiple tests, and also requires prolonged counting times for both subject and background readings at 24 hr. A more widespread application of the radionuclide technique for determining regional mucus transport therefore demands a more practicable means of assessing regional alveolar deposition.

This communication concerns a model for assessing mucus clearance from three lung zones: peripheral, intermediate, and inner (perihilar). The model takes into account regional alveolar deposition and the need to correct inner- and intermediate-zone retention data for particles passed into these zones from more distal airways. It is based on the concept that a Kr-81m ventilation image may be used to estimate the distribution of regional alveolar deposition, while a simple but sensitive counter system may be used to determine the total

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For reprints contact: J. E. Agnew, MSc, Dept. of Med. Phys., Royal Free Hospital, Pond St., London NW3 2QG.

\* Present address: Derby Chest Clinic, Green Lane, Derby ED1 1RX, England.



**FIG. 1.** Schematic outline of model. A is peripheral zone, B is intermediate zone, C is inner zone, and D is central zone (trachea and parts of main bronchi). Cross-hatched areas represent alveolar deposition. Arrows represent transport of particles on airways mucus.

amount of alveolar deposition. The reason why the distribution of inhaled Kr-81m should match that of radioaerosol alveolar deposition is that both relate to the distribution of readily ventilated airspaces in the lung. Krypton-81m can reach only the readily ventilated lung because of its short (13-sec) half-life. Aerosol particles that reach the terminal bronchioles tend to travel little farther because of efficient deposition by gravitational sedimentation in the alveolated airspaces.

Correcting for alveolar deposition essentially means subtracting the correct background from the activity-time curves corresponding to each of the three lung zones analyzed. The total amount of background for all three together is directly measurable—except insofar as differences of geometrical counting efficiency between the gamma camera and the counter system may introduce some error. It is the distribution of background between the three zones that is in question, and this distribution is taken to be the same as that of inhaled Kr-81m gas. If this assumption should prove false, then too much background would be subtracted from one activity-time curve and too little from another. Subtraction of too little background would lead to retention curves suggesting slower clearance than is truly the case. Subtraction of too great a background would lead to the opposite error. In particular, for subjects with high clearance rates, subtraction of too much background would be likely to yield negative retention values.

The model also proposes that retention in the inner and intermediate lung zones should be expressed as a percentage of the total input to the zone in question. Total input is calculated as the sum of initial deposition plus activity transported into the zone from airways situated peripheral to it. The essential details of the model are summarized in Fig. 1. In the peripheral region (Zone A) alveolar deposition (shown cross-hatched) is at its highest. The proportion of particles available for transport on mucus is therefore lower than in the other regions. In the inner, perihilar region (Zone C), alveolar deposition is likely to be much lower with, correspondingly, a larger number of particles available for

transport on mucus. The arrows connecting the regions denote transfer of particles deposited on mucus.

Regional mucus clearance of normal control subjects was compared with data from subjects expected to show impaired clearance, namely patients with mild to moderate stable asthma (4). The results obtained were inspected (a) to see whether any significantly negative retention values were obtained (which would imply oversubtraction of the alveolar deposition background), and (b) to see if the asthmatic subjects showed the slow clearance expected on pathophysiological grounds.

Two further checks were carried out on the “reasonableness” of the estimates of regional alveolar deposition obtained with the model. In the first, regional radioactivity distribution at 6 hr after inhalation in subjects having rapid clearance of the tracheobronchial airways was compared with the model’s alveolar deposition values. In the second, regional radioactivity distribution at 24 hr after inhalation was compared with the model’s values for four subjects who inhaled higher radioaerosol activities.

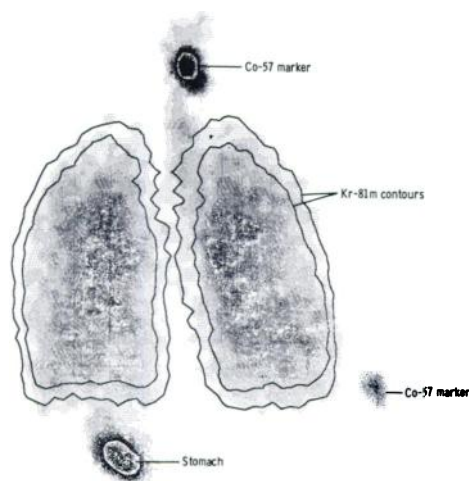
METHODS

**Subjects and data collection.** Details of the subjects studied are summarized in Table 1, together with lung function tests performed 10–20 min before radioaerosol inhalation. No normal subject had any history of asthma or chronic bronchitis. The asthmatic subjects were well stabilized on metered-dose inhaler bronchodilator therapy; none were on steroids at the time of study.

Preparation and administration of the radioactive particles have been reported previously (1,5). A spinning top generated 5- $\mu$ m-diam monodisperse ( $\sigma_g < 1.2$ )

**TABLE 1. SUBJECTS STUDIED**

	Control subjects	Stable asthma
No. of subjects	10	10
male	6	6
female	4	4
nonsmokers	8	7
ex-smokers	2	2
current smokers	0	1
Age		
mean	39	43
range	18–72	20–61
Forced expiratory volume in 1 sec (l)		
mean	3.6	2.4
range	2.2–5.4	1.4–3.5
Forced vital capacity (l)		
mean	4.3	3.5
range	2.4–6.9	2.0–6.2
Maximal expiratory flow at 50% vital capacity (l/sec)	4.2	1.7
	3.4–5.2	0.8–3.1



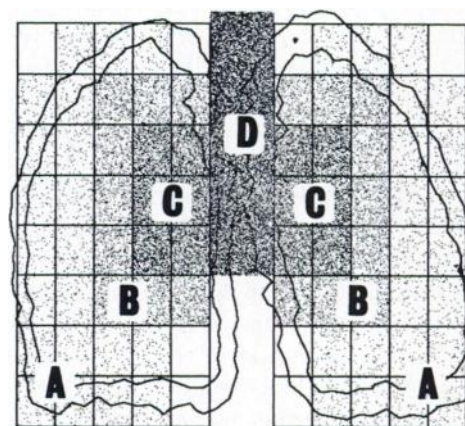
**FIG. 2.** Alignment of aerosol image (normal subject) and contours (15% and 30%) of Kr-81m ventilation image. Contour lines define approximate outer limits of Kr-81m image.

spheres of polystyrene labeled with Tc-99m. These were inhaled in a series of slow, 450-ml inhalations, each followed by a 3-sec breath-hold to permit particle sedimentation in the more distal airways. Initial lung radioactivity was approximately 27  $\mu\text{Ci}$  (1 MBq). Twin scintillation probes (5), mounted on a gantry in front of and behind the subject's chest, recorded total lung radioactivity 2–4 min after inhalation, and again at 6 and 24 hr. Graduated scales on the gantry enable the height and separation of the probes, relative to a fixed seat, to be reproduced for repeat measurements in any one subject. Posterior gamma-camera† images, each with a total of 40,000 counts, were recorded 10–15 min after inhalation and then at approximately 1, 2, 4, and 6 hr after inhalation. The acquisition times ranged from 2 to 10 min at the beginning of the test, 5 to 25 min at 6 hr after inhalation. The 40,000-count images were of poor statistical quality as images but were used only for analysis of data from relatively large lung zones. In some tests, additional readings were performed at 30–40 min and about 5 hr after inhalation. The camera was also in use for routine nuclear medicine investigations, so the exact timing of radioaerosol imaging was affected by the need to fit in with the routine program. A 5- or 10-min background reading was recorded either with the subject (before radioaerosol inhalation), or with a member of staff (who had not that day handled any radionuclide doses), seated in front of the camera. During imaging each subject wore two small Co-57 marker sources attached to marker tapes worn continuously throughout the 6-hr observation period. These tapes were positioned over the lower cervical spine and laterally over a lower right rib; the marker positions could thus be seen clearly on the Tc-99m images without intruding on the actual lung images. Each subject also had a posterior Kr-81m ventilation image (200,000 counts) immediately followed by an image (5,000 or 10,000 counts) of the Co-57

marker sources. The Kr-81m was administered through a lightweight mask during tidal breathing. All camera images were recorded in  $64 \times 64$  format in a V77-200 computer system.†

**Analysis of data.** Using the computer's display system, the position of the Kr-81m image (and of the data corresponding) was adjusted horizontally and vertically until aligned with the initial aerosol image. Two criteria had to be met for satisfactory alignment: superimposition of the marker source images, and visualization of the aerosol image within the outer (15% and 30%) contours of the Kr-81m image (Fig. 2). These contour lines represent activity high enough to exclude background but low enough to include most of the Kr-81m activity. The later aerosol images were then aligned with the Kr-81m image, and thereby with the first aerosol image. Division of the lung image into inner, intermediate, and peripheral zones was based on fitting a  $5 \times 8$  matrix as closely as possible to the outer contours of the Kr-81m image, as illustrated in Fig. 3. To avoid interpolation, the overall dimensions of the  $5 \times 8$  matrix were chosen so that each cell corresponded to an integral number of the  $64 \times 64$  cells used for data collection. For each aerosol image, and for a copy of the background image shifted to the same extent horizontally and vertically, total counts were determined in Zones A, B, and C—and for the sum of both  $5 \times 8$  matrices plus the central Zone D. These counts were then expressed as count rates (using counts per 100 sec as a convenient unit) corrected for background and radionuclide decay. The values thus obtained provide the basis for all further calculations but themselves relate only to “whole-lung retention,” corrected neither for alveolar deposition nor for transport from one region into another.

Krypton-81m counts in Zones A, B, and C, expressed as a percentage of the total in both  $5 \times 8$  matrices plus center Zone D, were used to predict the proportion of alveolar deposition expected in these three zones. Readings from the probe system (corrected for background and decay) gave values of total Tc-99m lung



**FIG. 3.** Definition of Zones A-D relative to Kr-81m contours shown in Fig. 2.

retention at 6 and at 24 hr after inhalation. A gamma-camera estimate of 6-hr retention (relative to the initial base line at 10–15 min after inhalation) was obtained from the count rate summed over the two  $5 \times 8$  matrices plus center zone D. This was translated into an estimate of 24-hr retention for the camera system by multiplying it by the ratio of the probe system's 24-hr to 6-hr retention values. Total 24-hr retention thus estimated was multiplied by the Kr-81m predictions for the proportion of alveolar deposition to be expected in each region. This gave estimates for the count rate in each of Regions A, B, and C due to alveolar deposition. Subtracting this alveolar component from the previously calculated "whole-lung" count rates then gave values for each region for the "airways" count rate corresponding to particles deposited in the mucus-bearing ciliated airways.

To correct for interregion transport of particles, the base line (100%) count rates for inner (C) and intermediate (B) zones were recalculated for the data from each sequential image as the initial count rate plus the cumulative loss in count rate from the more peripheral zones. Thus, at any time  $t$  at which an image was recorded, the 100% count for Zone C was the sum of the initial count rate in C plus the amount by which the count rate in Zones A plus B had decreased up to time  $t$ . Similarly the 100% count rate for Zone B was the sum of the initial count rate in B plus the count rate lost from Region A up to time  $t$ . The correction for interregion transport of particles could be applied to either "whole-lung" or "airways" data; the results presented are based on applying it to "airways" data.

As readings were not taken at exact hourly intervals from inhalation, linear interpolation was used to calculate percentage retention for each subject at 1, 2, 3, 4, 5, and 6 hr after inhalation. This was performed for the "whole lung" data, not corrected for alveolar deposition or for interzone transport, and for the "airways" data corrected for both factors.

**Experimental checks on the model estimates of regional alveolar deposition.** Some normal subjects achieve virtually complete tracheobronchial clearance by 6 hr from inhalation, even with peripherally deposited particles. Regional retention at 6 hr should then approximate regional alveolar deposition. Data were available from six normal subjects with at least 90% tracheobronchial clearance over the 0- to 6-hr period; there were four tests from the main study plus repeat tests at higher inhalation flow rates (giving less peripheral deposition) in two further subjects from the main study control group. Retention at 6 hr in each lung zone was expressed as a percentage of the initial deposition in that zone for comparison with the model-based estimates of regional alveolar deposition. Retention values lower than the model estimates would imply oversubtraction of background in the model.

Direct measurement of regional alveolar deposition in terms of retention at 24 hr was attempted in four subjects whose initial lung radioactivity was approximately  $81 \mu\text{Ci}$  (3 MBq)—three times the activity used in the main study. Readings of Tc-99m retention (25,000–55,000 counts) were recorded for 40 or 60 min duration, and were followed by a background reading of similar duration. Again the basis of comparison with the model estimates of alveolar deposition was that if regional retention values at 24 hr were significantly lower than the model values, then oversubtraction of background in the model would be inferred.

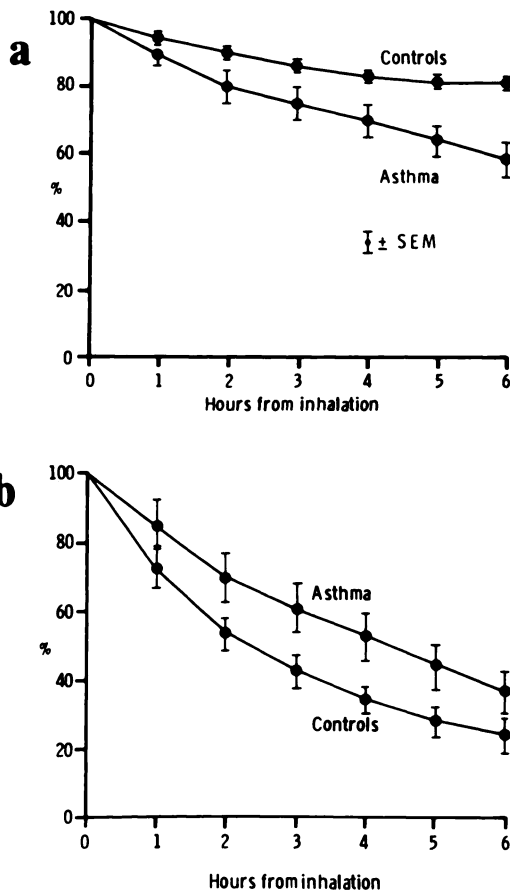
## RESULTS

Mean inhalation flow rate in the asthmatic subjects (26 l/min, range 16–31) was similar to that in the control subjects (27 l/min, range 14–50). Despite this, the probe system's 24-hr retention measurements showed much lower mean alveolar deposition in the asthmatic subjects (22%, range 13–33%) than in the control subjects (57%, range 43–67%). Thus on average, nearly 80% of particles in the asthmatics, but only just over 40% in the control subjects, were deposited on mucus-bearing airways and cleared from the lung within 24 hr.

Figure 4 illustrates particle retention in Zone A, the peripheral zone. This is expressed first (a) in terms of the uncorrected "whole lung" data, which suggest lower retention (faster clearance) in the asthmatic subjects than in the control subjects, and second (b) in terms of "airways" data corrected for regional alveolar deposition. The "airways" data demonstrate significantly higher retention (slower clearance) in the asthmatic subjects.

Figure 5 illustrates particle retention in Zone C, the inner zone. This similarly is expressed (a) in terms of the uncorrected "whole lung" data—suggesting little difference between asthmatic and control subjects for clearance over the first 4 hr, then slightly greater clearance in the asthmatics—and (b) in terms of "airways" data corrected for regional alveolar deposition and for transfer of activity from Zones A and B into Zone C. The "airways" data suggest markedly impaired clearance in the asthmatic subjects.

Retention in Zone B was generally similar to that in Zone C; the "airways" data are summarized in Table 2. The "whole lung" data for this zone showed one value for 1-hr retention in excess of 100%; this also occurred for the whole-lung Zone C data of two subjects (both asthmatic; retention values 107% and 120%, respectively). The lowest Zone B airways retention value observed at 6 hr was 2%, but four control subjects had 6-hr Zone C airways retention of less than zero (actual values  $-0.5$ ,  $-1$ ,  $-1$ , and  $-1.5\%$ ). The lowest 6-hr Zone C retention in an asthmatic subject was  $+0.5\%$ . Thus the "whole lung" data showed occasional retention values for inner and intermediate zones close to or in excess of



**FIG. 4.** Peripheral zone (Zone A) retention of aerosol: (a) whole-lung data (no correction for alveolar deposition), (b) "airways" data, corrected for alveolar deposition. Error bars indicate  $\pm$  s.e.m.

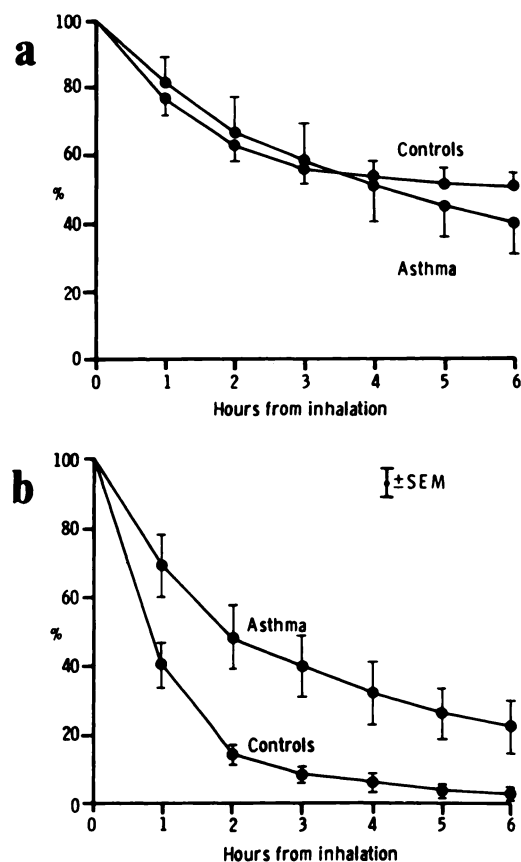
100% during the early stages of clearance, and by 6 hr after inhalation the "airways" data showed occasional minimally negative retention values for the inner zone. No major negative excursions were seen in any subject's calculated retention.

In the six subjects with greater than 90% tracheobronchial clearance over the 0- to 6-hr period, mean Zone A retention at 6 hr was 4.2% (s.d. 4.4%) greater than the model value for alveolar deposition; for Zone B the mean difference between 6 hr retention and predicted alveolar deposition was 5.9% (s.d. 4.8%); and for Zone C it was 0.7% (s.d. 1.9%).

Good general agreement was seen (Table 3) between the model estimates of alveolar deposition and the 24-hr retention readings in the four subjects inhaling higher radioaerosol activities. The model overestimated Zone A alveolar deposition in a patient with airways obstruction, and overestimated Zone C alveolar deposition in a normal nonsmoker and an asymptomatic smoker (Table 3).

DISCUSSION

To date, the gamma camera has been little exploited for studying mucus clearance from different lung re-



**FIG. 5.** Inner zone (Zone C) retention of aerosol: (a) whole-lung data (no corrections), (b) "airways" data, corrected for alveolar deposition and for transport of particles into Zone C from Zones A and B. Error bars indicate  $\pm$  s.e.m.

gions. A major difficulty has been distinguishing activity of the airways from that beyond the reach of the mucociliary escalator. This may not matter when patients with extremely slow mucus transport are compared with normal subjects (6) or when the patient acts as his own control in studies of drug or physiotherapy effects on regional clearance (7-11). But whenever the activity in any region is substantially due to alveolar deposition, correction should be made for this before assessing mucus transport (12,13). The practical effect of so doing is borne out by our results. Impaired clearance in asthmatic subjects was shown by "airways" retention but not by "whole lung" retention.

**TABLE 2. "AIRWAYS" RETENTION CORRECTED FOR INTERZONE TRANSFER: ZONE B (MEAN  $\pm$  s.e.m.)**

Time from inhalation (hr)	Control subjects	Stable asthma
1	51 $\pm$ 6	74 $\pm$ 8
3	17 $\pm$ 2	43 $\pm$ 8
6	10 $\pm$ 2	23 $\pm$ 6



**TABLE 3. REGIONAL ALVEOLAR DEPOSITION: COMPARISON BETWEEN RETENTION AT 24 hr AND MODEL VALUES**

Subject no.	Regional alveolar deposition as % of initial deposition in zone					
	Inner zone		Intermediate zone		Outer zone	
	24-hr reading	Model estimate	24-hr reading	Model estimate	24-hr reading	Model estimate
1*	48.5	52.4	67.9	67.0	80.7	76.8
2†	46.2	46.4	57.8	53.8	71.5	70.4
3‡	40.5	46.2	55.9	55.8	69.2	66.6
4§	19.9	19.1	24.7	30.4	42.8	53.4
Mean	38.8	41.0	51.6	51.8	66.0	66.8

\* Normal nonsmoker (FEV<sub>1</sub> 95% predicted).  
 † Asymptomatic ex-smoker (FEV<sub>1</sub> 135% predicted).  
 ‡ Asymptomatic smoker (FEV<sub>1</sub> 106% predicted).  
 § Chronic obstructive airways disease (FEV<sub>1</sub> 61% predicted).

Substantial evidence exists that mucus clearance really is impaired in asthma (4). Tracheal mucus transport is abnormal in elderly stable asthmatics (14) and in asymptomatic young patients with allergic asthma (15); tracheobronchial clearance is impaired in mild asthma (13). Loss of ciliated columnar cells from the bronchial mucosa occurs in asthma together with mucus plugging of the airways; this affects airways of all sizes in patients who die in status asthmaticus, but only peripheral airways in asymptomatic asthmatics who die from other causes (16).

An important practical assumption made in the model is that a Kr-81m ventilation image genuinely maps out the distribution of alveolar deposition. With its short (13-sec) half-life, Kr-81m (unlike Xe-133) reaches only the "readily ventilated" lung (airspace reached by inspired gas within a few respiratory cycles), not the entire resident gas volume (17). Radioaerosol particles likewise reach only the "readily ventilated" lung; particles that reach the lung acini are rapidly deposited there by gravitational sedimentation. If the proportion of Kr-81m in one zone were lower than the true proportion of alveolar deposition, then in at least one of the other two zones it would be higher. Subtracting too high an estimated alveolar-deposition background would be likely to give substantially negative airways retention values in subjects whose tracheobronchial clearance was nearly complete by 5-6 hr after inhalation. This did not occur. The data from the subjects with rapid tracheobronchial clearance, and the 24-hr regional readings in two of the four subjects, suggest that the model may slightly overestimate innerzone (Zone C) alveolar deposition. This could result from Kr-81m activity in the larger bronchi; alveolar deposition, by definition, excludes any contribution from these. Nevertheless, the lack of any significantly negative values for airways retention and the

good general agreement seen at 24 hr (Table 3) suggest that the Kr-81m distribution does provide a valid estimate of regional alveolar deposition.

A few patients with airways obstruction will not complete their tracheobronchial clearance within 24 hr (1). Using 24-hr retention as alveolar deposition would then lead to falsely low values for "airways" retention. Probably this is important only when airflow obstruction is more severe than in the asthmatic subjects we studied. With a sufficiently sensitive counter, a retention measurement at 48 hr could be used to estimate alveolar deposition (1).

Differing deposition patterns are important when one is comparing normal clearance with that in airways obstruction, in which poor lung penetration of inhaled aerosols occurs. Essentially, airways narrowing increases linear airflow velocities and irregularity of flow profiles, thereby enhancing deposition by inertial impaction. Thus, alveolar deposition was dramatically reduced in the asthmatic subjects. Their maximal flow at 50% vital capacity, which responds to small-airways narrowing, was also reduced.

Reduced particle penetration implies shorter mean path lengths for clearance from the lung but gives no insight into distribution within each lung zone. Five-micron particles inhaled by normal subjects at 20-30 l/min deposit in the more proximal small airways primarily by impaction, and in the more distal small airways primarily by sedimentation (18). Airway narrowing enhances impaction but reduces sedimentation (18). Small-airways narrowing in asthma should thus cause a proximal shift of deposition within the peripheral zone. This makes the model's ability to demonstrate retarded peripheral clearance in asthma (Fig. 4) more striking than might at first appear, since the mean lengths of clearance path from deposition sites to points of exit from

the peripheral zone were probably shorter in asthmatic than in control subjects. The effect of airways obstruction on the distribution of deposition within the large airways is not well understood at present (19). Our asthmatic subjects, however, did not have marked air-flow limitation in the large airways, so that their large-airways distribution is unlikely to have been grossly abnormal. Impaired clearance from peripheral and intermediate zones implies delayed input from them into the inner zone but, since peripheral-zone deposition was low, the effect is likely to have been small.

Our model assumes unidirectional mucus transport from the periphery to the trachea, ignoring the possibility of retrograde (20) transport. All subjects, however, showed decreasing peripheral retention over the whole 6-hr observation period. Any possible transient retrograde transport was probably swamped by overall transport towards the trachea.

Radioaerosol techniques using soluble particles are increasingly coming into the nuclear medicine repertoire for ventilation imaging. Radionuclide imaging with insoluble particles could also play a significant role in assessing ciliary function. We propose our model as a practical approach to assessment of mucus transport in different lung regions. Intervening use of the gamma camera for other investigations is possible. The procedure requires computing facilities and access to Kr-81m. Xenon-133 images might not be appropriate unless restricted to the early wash-in stages. The model is equally applicable to mucus transport by mucociliary action or by cough. With a dedicated gamma camera, more-frequent imaging would provide better data about the timing of mucus clearance events, particularly those due to cough. Provided that care is taken over patient positioning and image alignment, smaller analysis zones could give more detailed topographic information about mucus transport. The extent to which these possibilities would justify the extra work involved we leave to other investigators. Application of the model in the present study has, we believe, demonstrated that mucus transport is quite seriously impaired in the peripheral, intermediate, and inner airways of patients with stable asthma.

#### FOOTNOTES

† International General Electric Maxicamera.

‡ Nodcrest Medical Systems.

#### ACKNOWLEDGMENT

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