Deposition and Clearance of 2 μ Particles in the Tracheobronchial Tree of Normal Subjects—Smokers and Nonsmokers

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ABSTRACT Deposition and clearance of inhaled particles of iron oxide labeled with ^{198}Au were studied in 19 normal subjects (10 nonsmokers and 9 smokers). For this purpose, monodisperse aerosols of particles with a 2 μ diameter were produced in a spinning disc atomizer. Thoracic counts and images with a scintillation camera were begun immediately after inhalation of the aerosol and continued for 6 hr.

In all subjects, smokers and nonsmokers, the deposition of the particles was uniform throughout both lung fields, with approximately half of the particles deposited in the ciliated airways (tracheobronchial deposition) and half in the nonciliated airways (alveolar deposition).

Tracheobronchial clearance in nonsmokers occurred immediately after inhalation, first at a fast rate for particles deposited in the largest and most central airways, and then at a slower rate for particles from the smaller and more peripheral airways. Photoscintigrams showed that the particles cleared steadily with no retention in any area. The general pattern of clearance may be likened to a model of multiple conveyor belts with speed increasing from the peripheral to the central airways in such a way as to prevent "particle jams" at airway confluence points.

In smokers, tracheobronchial clearance was delayed for periods of 1–4 hr after inhalation. Furthermore, in contrast with the findings in nonsmokers, significant clearance was still occurring in many of the smokers in the 5th and 6th hr after inhalation. Also, photoscintigrams showed an abnormal accumulation of particles in the large airways several hours after inhalation of the aerosol.

INTRODUCTION

It has been recognized for some time that the transport of mucus by the cilia of the tracheobronchial epithelium is an important mechanism for the removal of inhaled particulate matter (1, 2). In an environment in which noxious materials exist in dangerous quantities, such transport plays a major role in the defense against disease. Thus, it may be said that normal mucociliary activity is essential for the maintenance of healthy lungs.

One method of assessing mucociliary activity is to study the clearance of inhaled particles. In man, such a study may be approached by monitoring radioactivity in the thorax after inhalation of labeled material as described by Albert and Arnett (3). Since their report, other investigators have used either heterodisperse (4–6) or monodisperse (7) aerosols of radioactive substances with particle size ranging from 1 (5) to 40 μ (4). In these investigations radioactivity was monitored with from one to seven scintillation detectors and quantitative clearance curves determined. Although these studies resulted in valuable information, simultaneous images of the distribution and clearance of inhaled particles were not obtained. Images are, however, important in the following two ways: first, the pattern of clearance of particles from the tracheobronchial tree is dependent on the site of deposition (8), so that any analysis of clearance curves should take images of deposition into account; second, visualization of the process of clearance may point out abnormalities which an analysis of values may overlook. Besides not providing an image, a scintillation detector can only give information on a limited

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TABLE I

Vital Statistics, Smoking Habits, and Respiratory

Subject	Sex	Age	BSA	Smoking habits		Total lung capacity	
		yr	m^2	*packs per day*	*yr*	*ml*	*% predicted**
D. J.	M	22	1.76	—	—	6160	89
B. H.	M	25	1.86	—	—	6700	95
R. F.	M	27	1.60	—	—	4610	65
P. A.	M	23	1.90	—	—	6390	99
A. S.	M	25	2.02	—	—	7790	117
W. M.	M	22	2.08	—	—	7090	99
F. W.	M	22	1.88	—	—	5940	85
S. E.	M	32	1.73	—	—	6390	104
V. L.	M	42	2.18	—	—	7720	114
B. K.	M	36	2.02	—	—	6420	104
W. B.	F	44	1.80	1	5	5720	118
J. E.	M	29	2.06	1	12	8580	110
A. C.	F	46	2.00	1	5	4880	105
D. U.	M	23	1.94	$\frac{3}{4}$	5	6070	96
M. W.	M	30	1.99	$\frac{3}{4}$	10	6110	99
D. K.	M	23	1.78	1	6	5910	92
W. F.	M	47	1.60	$1\frac{1}{2}$	27	5220	81
B. C.	M	22	1.72	$1\frac{1}{2}$	$5\frac{1}{2}$	4940	110
A. L.	F	19	1.58	$\frac{1}{2}$	2	4090	83
Nonsmokers							
Average		27.6	1.90			6521	97.1
SE		2.2	0.06			290.0	4.8
Smokers							
Average		31.4	1.83			5724	95.6
SE		3.7	0.06			420.1	4.6

* Percentage of the predicted values obtained from Needham, Rogan, and McDonald (11).
‡ Percentage of the predicted values obtained from Kory, Callahan, and Boren (12).
§ Percentage of the predicted values obtained with the formula by Burrows, Kasik, Niden, and Barclay (13).

region of the thorax, thus making the study of global lung clearance difficult.

The use of heterodisperse aerosols, valuable in the sense that aerosols in nature are never monodisperse, creates an additional difficulty in the analysis of clearance because of differences in the weight and site of deposition of particles of various diameters. Also, the large diameter particles used in some studies (4) do not permit the analysis of clearance from the small airways.

We studied normal subjects using a monodisperse aerosol; particles were produced of such a diameter (2 μ) that with an adequate air flow, a homogeneous dispersion throughout both lungs could be achieved. We used a scintillation camera and took photoscintigrams of initial deposition and followed the clearance by simultaneous counting and imaging. We also compared the patterns of deposition and clearance observed in those subjects who were smokers with those who were nonsmokers. Previous reports in smokers had demonstrated either normal (6, 9) or abnormally slow (10) clearance. This discrepancy could be explained on the basis of differences in the patterns of deposition and clearance of particles not detectable by the methods used.

METHODS

19 normal subjects were studied (16 males and 3 females). All had a negative history of respiratory or cardiac diseases, normal chest X-ray, and normal pulmonary auscultation. Vital statistics, smoking history, and respiratory function tests are shown in Table I. Nine of the subjects (including the three women) were cigarette smokers. None of the subjects was a pipe or cigar smoker. Pulmonary function tests were normal in both nonsmokers and smokers with the exception of slightly decreased lung volumes in subject R. F. and forced expiratory volume in A. C. and B. C. There were no statistically significant differences in any of the tests performed between nonsmokers and smokers

Function in the 19 Normal Subjects Studied

Vital capacity		Functional residual capacity		Maximum voluntary ventilation		Forced expiratory volume—1 sec	Diffusing capacity	
ml	*% predicted**	*ml*	*% predicted**	*l/min*	*% predicted‡*	*% VC*	*ml/min mmHg*	*% predicted§*
4570	92	3230	96	147	81	72	27.9	97
5080	100	3630	106	178	98	86	34.6	116
3340	71	2760	74	163	95	93	19.0	74
5090	103	2770	96	175	97	87	28.2	92
6090	118	3240	109	199	108	80	31.8	99
5820	106	2920	90	216	111	74	36.7	109
4680	91	2920	89	181	97	81	26.6	87
4640	110	2770	97	218	145	81	28.4	101
5420	114	2840	86	169	106	79	28.0	91
4250	89	3390	119	173	104	79	36.7	124
3540	99	2870	116	110	90	79	19.8	85
5550	99	4500	116	172	90	75	28.9	91
2900	84	2860	121	94	80	70	21.3	82
4590	93	2610	95	183	102	88	33.7	107
4630	100	2330	85	189	133	83	22.5	73
4480	94	3400	116	211	121	84	28.8	100
3310	82	3510	96	118	83	76	18.6	91
3930	84	2400	81	156	89	68	27.1	110
3230	92	2270	91	101	75	79	20.2	89
4898	99.4	3047	96.2	181.9	104.2	81.2	29.7	99.1
251	4.4	96.6	4.0	7.2	5.3	2.0	1.7	4.5
4018	91.8	2972	101.8	148.2	95.3	78.6	24.5	92.0
286	2.3	241.3	5.1	14.2	5.8	1.9	1.7	4.0

(see bottom of Table I). The average age of smokers, although slightly higher than that of nonsmokers, was not statistically different ($P > 0.1$).

Iron particles labeled with ^{198}Au were administered to all subjects. Iron oxide solution (Diamond Alkali; Diamond Alkali Research Center, Painesville, Ohio) was labeled with ^{198}Au and administered in the form of a monodisperse aerosol produced in a spinning disc atomizer (Technical Machine Co., Carmel, N. Y.) by methods based on those described by Albert, Petrow, Salam, and Spiegelman (14). With the atomizer shown diagramatically in Fig. 1, the diameter of the droplets in the aerosol can be varied by changing either the concentration of the solution used or the speed of the spinning disc. The disc speed was regulated through a frequency convertor (Tel-Instrument Electronics Corp., Carlstadt, N. J.) and tested with a strobe light (Strobotac; General Radio Company, Chicago, Ill.). Before and after each administration, samples of the particles were obtained in a cascade impactor (Casella, London, England) and the diameter measured under a microscope with a calibrated graticule. The mass median diameter of the particles used was 2.04 μ with a geometric standard deviation of 1.08. Particle density was measured with a Timbrell aerosol spectrometer and found to be 2.5 cm^3. The average lung radiation dose was 0.31 rads and the whole body dose 0.05 rads.

Before the administration of the aerosol the subject was trained to breathe at a frequency of 15 breaths/min, a tidal volume of 800 ml, and an average inspiratory rate of air flow of 30 liters/min. During the administration, the subject was seated and breathed, with a noseclip in position, through a mouthpiece connected to the atomizer. Inspirations followed a light timer set at 15 flashes/min; at the same time tidal volume was monitored with a pneumograph and rate of air flow with a constant temperature anemometer (Thermo-Systems, Inc., St. Paul, Minn.).

The aerosol was inhaled for 5 min, and counting and imaging of the radiation in the thorax were begun immediately. For this purpose (see Fig. 2) the subject was positioned with his back against the crystal of an Anger scintillation camera (Pho Gamma III; Nuclear-Chicago Corporation, Des Plaines, Ill.). Special care was taken to insure that the subject was kept in the same position in relation to the camera for the duration of the study. A 1000 orifice collimator with an 11 in. diameter and a thickness of 3 in. was used, and the camera was set with a 20% window around the peak energy of 412 kev. Serial pictures of 5 min duration were taken every 10 min. Counts and images were recorded for 6 hr on the 1st day and again at 24 hr after inhalation. Corrections for physical decay of the isotope were performed in all measurements. Clearance curves were drawn using the first counts after inhalation as 100% and the remaining counts as percentages thereof.

Clearance was measured in all subjects between 10:00 a.m. and 4:00 p.m. on the 1st day and at 10:00 a.m. on the 2nd day. During the measurement and for 2 hr before, none of the subjects smoked. A light meal was served at 1:00 p.m., and no other food or drink was allowed during the study. During the measurements the room temperature varied between 72° and 78°F and the humidity between 32 and 47%.

RESULTS

Deposition

Immediately after inhalation there was, as seen in the zero-hour photoscintigrams (Figs. 3 and 4), homogeneous dispersion of the particles in both lung fields.

Roughly half of the particles were deposited in the nonciliated respiratory airways, as indicated by the counts obtained at 24 hr after inhalation (last column, Table II). The pattern of deposition shown in the zero hour photoscintigrams and by the counts at 24 hr, were similar in nonsmokers and smokers. Also, the radioactivity immediately after inhalation (Table II, first column) was not statistically different in the two groups of subjects.

Clearance

The data for nonsmokers and smokers are presented separately as clearance was markedly different.

Nonsmokers. The results are summarized in the upper part of Table II. During the time of observation, as exemplified by subject P. A. in Fig. 3, the particles cleared steadily and evenly without retention in any area. In three subjects (D. J., F. W., and B. K.) with very high initial counts, there was visualization of the trachea and/or main bronchi during the 1st hr of clearance (Fig. 5).

In the majority of the subjects, the fastest clearance rate was achieved during the 1st hr (average 18.5% of the initial count); during the next 3 hr, clearance was

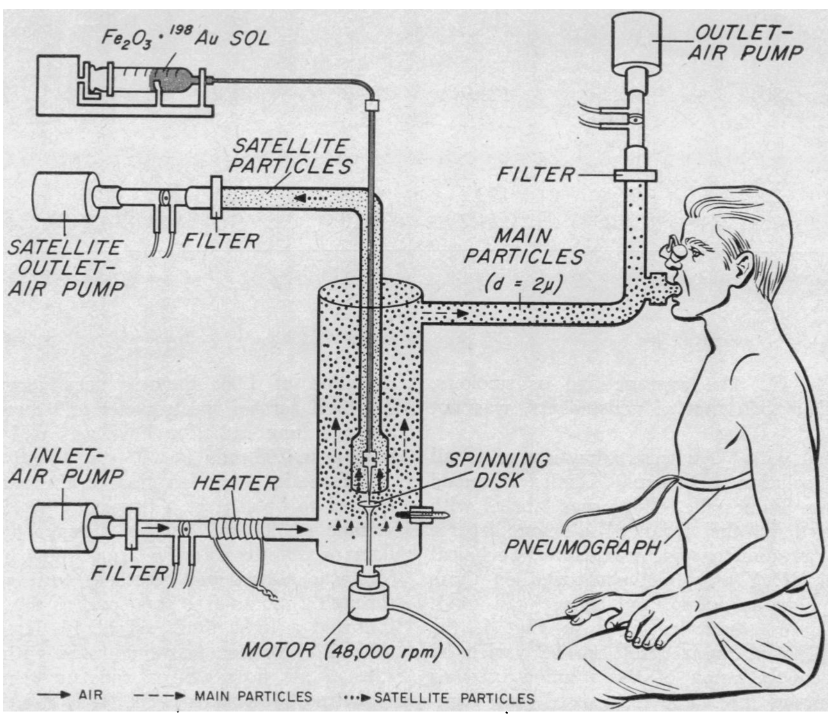

FIGURE 1 Spinning disc atomizer for the production of monodisperse aerosols. A solution of iron oxide labeled with ^{198}Au is ejected with a constant flow infusion pump on to the center of a small spinning disc. A film forms on the surface of the disc and breaks up into particles on the periphery. A heated current of air from the inlet pump dries the particles, reduces their size, and carries them to the subject while the smaller and nonuniform satellite particles are removed through a separate outlet. For this study the diameter of the particles was approximately 2 μ.

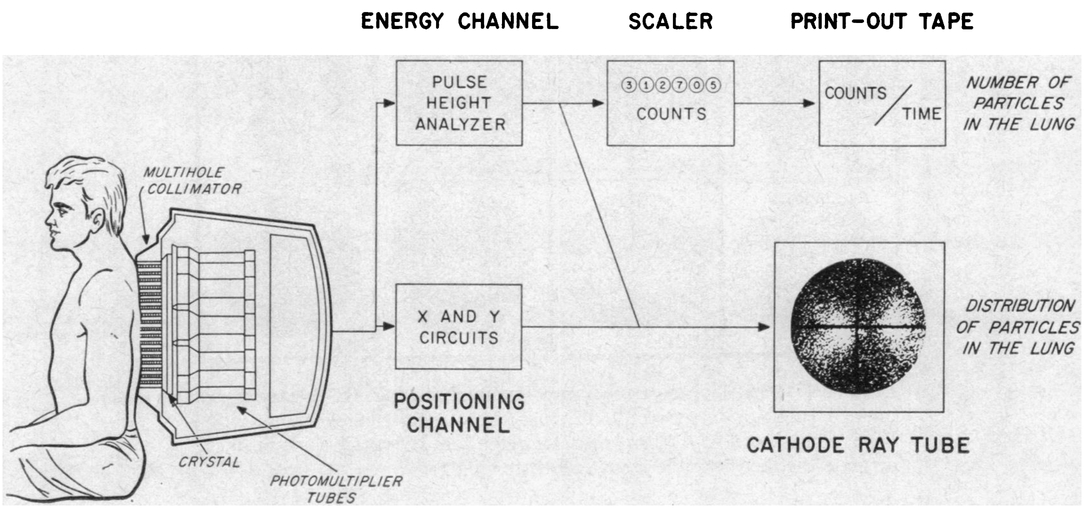

FIGURE 2 Counting and imaging of inhaled particles. The gamma photons emitted by the radioactive gold retained in the lungs of the subjects pass through a multihole collimator and strike a sodium iodide crystal. The burst of light produced is then amplified in photomultiplier tubes. The resultant energy is discriminated in a pulse height analyzer, and the events of appropriate energy are displayed as counts per unit of time on a scaler and recorded on tape. These counts are proportional to the total number of particles retained in the lung. The energy impulses also pass through a X and Y positioning channel and are displayed on a cathode ray tube and photographed with a Polaroid camera. In the photographs the white spots correspond to the gamma photons from the particles, so that the pattern formed represents the distribution of inhaled particles in the lungs.

much slower (7.0, 7.1, and 4.2% per hour), and in the 5th and 6th hr, there was no measurable clearance in 7 of the 10 subjects. The other three subjects showed clearance in the 5th hr, but in the 6th hr in only one (B. K.) was clearance still measurable. This subject also demonstrated the lowest 24 hr retention of all nonsmokers, indicating a more central deposition of the inhaled particles than the other subjects; B. K. had had a chronic sinusitis with postnasal drip for many years which might account for these results.

24 hr retention for all nonsmokers averaged 48.3% of the initial counts, and in the subjects in whom measurements were performed at 48 and 72 hr there was no significant decrease from the value at 24 hr other than that due to physical decay of the isotope.

In all subjects the particles were swallowed with a corresponding appearance of radioactivity in the stomach. Radioactivity was present in the feces for 2 days after inhalation. No radioactivity was detectable in the blood.

Smokers. The results for smokers are indicated in

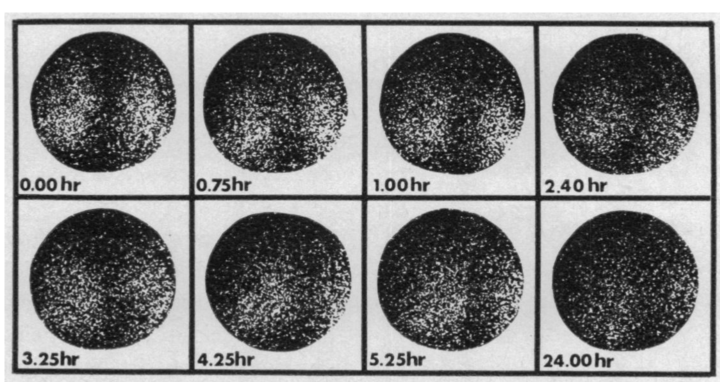

FIGURE 3 Serial photoscintigrams obtained during clearance of inhaled particles in P. A., a nonsmoker. The number represents time after inhalation. Each photoscintigram was recorded for a period of 5 min. After a well dispersed bilateral deposition shown at 0.00 hr, the particles cleared evenly without appreciable regional retention.

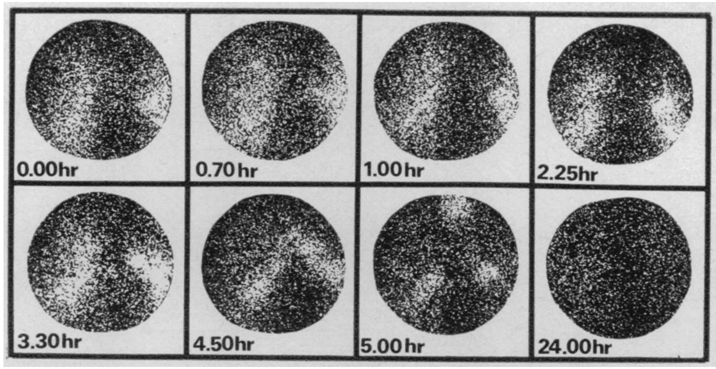

FIGURE 4 Serial photoscintigrams obtained during the clearance of inhaled particles in subject J. E., a smoker. After homogeneous initial deposition shown at 0.00 hr, there is retention of particles in the large airways distinctly visible from 2.25 hr to 5.00 hr.

the lower part of Table II. Significant differences from nonsmokers were found during clearance. Thus, photoscintigrams demonstrated that clearance was not as steady and uniform as that in nonsmokers; moreover, the photoscintigrams showed an accumulation of particles in large airways several hours after inhalation (compare photoscintigrams taken during the 2nd, 3rd, 4th and 5th hr after inhalation in Figs. 3 and 4). Unlike the findings in nonsmokers, visualization of the trachea and main bronchi was observed in all subjects; furthermore, it appeared late in the clearance process (Fig. 5) and was not related to the initial number of counts.

Percentage of initial counts obtained at hourly intervals (Table II) also demonstrated differences in clearance between smokers and nonsmokers. Thus, at the end of 1 hr, smokers had cleared only 2.6% of the initial count, as compared with 18.5% for nonsmokers (this difference was statistically significant, $P < 0.001$); during the 2nd, 3rd and 4th hr the clearances of 5.8, 5.9, and 7.2% respectively, were not significantly different from those found in nonsmokers. In the 5th hr there was still measurable clearance in 8 of the 9 smokers as compared with 3 of the 10 nonsmokers, and in the 6th hr, 5 smokers were still clearing, whereas only one nonsmoker (B.K.) was still showing clearance.

The average retention of 46.8% at 24 hr was not significantly different from that found in nonsmokers (48.3%). Also as in nonsmokers, there was no appreciable clearance during the 2nd and 3rd day after inhalation.

There was no relationship between number and type of cigarettes smoked and number of years of smoking and the alterations found.

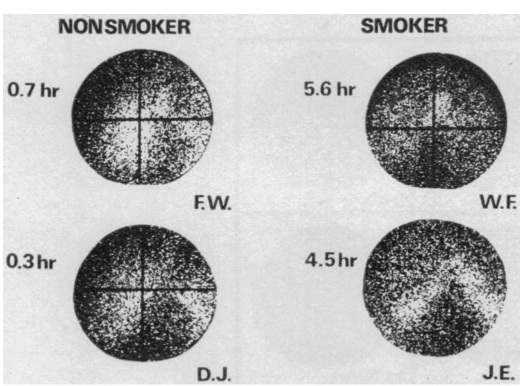

FIGURE 5 Visualization of trachea and main bronchi in normal subjects. In the nonsmokers the large airways appeared during the 1st hr after inhalation whereas in the smokers they appeared much later (in the present examples at 4.5 and 5.6 hr).

DISCUSSION

Our results show similar deposition patterns for nonsmokers and smokers, but there were marked differences in their clearance patterns.

Distribution of aerosols in the lungs is dependent on the diameter and density of the particles used and on the pattern of breathing present during inhalation (8, 15). Other factors that may play a role are related to the presence of obstruction to air flow caused by either bronchoconstriction, swelling of the bronchial mucosa, or secretions in the airways (8). Particles and pattern of breathing were the same for all subjects studied, and the clinical and standard physiological data did not suggest abnormalities in the airways of any of the subjects. Thus, the deposition of particles, as assessed by the examination of the first photoscintigrams after inhalation, was similar for all subjects, both smokers and nonsmokers. These photoscintigrams showed a homogeneous distribution with particles in both the central and peripheral portions of the lung fields.

If clearance obtained during the first 24 hr after inhalation corresponds to particles deposited in the ciliated tracheobronchial tree (7), our study showed that particles were more or less evenly distributed between ciliated and nonciliated airways and also that distribution was similar for nonsmokers and smokers. Our findings, of significant clearance being evident only on the 1st day after inhalation, also suggest that the particles cleared during this time were those deposited in the ciliated epithelium of the tracheobronchial tree. No attempt was made to measure the clearance of particles deposited in nonciliated respiratory airways. This clearance (alveolar) has been reported (5, 7) to last between 130 and 150 days.

Transport of particles in the tracheobronchial tree is not only dependent on mucociliary activity, but also on the presence of cough and the pattern of breathing (16). None of the subjects coughed during the study, and no marked deviation of the normal pattern of ventilation was found in measurements made during the monitoring of clearance.

In nonsmokers tracheobronchial clearance began immediately after inhalation of the particles. At first, particles were cleared at a fast rate, corresponding to those deposited in the largest and most central airways. Later, particles from the smaller and more peripheral airways were cleared at a slower rate. The relationship between site of deposition and rate of clearance is confirmed by other studies that showed: an initial rapid decrease of radioactivity in the medial part of both lungs after inhalation of labeled particles (17), and an increment in the number of particles cleared rapidly after inhalation, when particle size was big enough to cause deposition mainly in the large airways (7).

In all cases, the amount of particles deposited in a particular region of the lung seemingly does not alter the clearance time for this region, eliminating any possibility of a single power function to describe total clearance of the lungs (5). Also, this indicates that within certain limits, load does not change mucociliary activity, a fact which is compatible with an escalator or conveyor belt model to explain tracheobronchial clearance: as with an airport conveyor belt the speed is in-

TABLE II
Deposition and Clearance of 2μ Particles in 19 Normal Subjects

Subject	Initial counts per minute	Percentage of initial count cleared in each hr after inhalation						Retention at 24 hr
		1st	2nd	3rd	4th	5th	6th	
Nonsmokers								
D. J.	1493	32	6	7	0	0	0	52
B. H.	1100	20	5	1	3	5	0	60
R. F.	754	22	7	0	2	0	0	60
P. A.	1333	20	9	3	12	0	0	42
A. S.	1284	8	10	14	4	0	0	53
W. M.	858	20	10	7	0	0	0	52
F. W.	2071	23	0	2	7	0	0	45
S. E.	1159	10	14	10	1	6	0	49
V. L.	765	18	9	18	12	0	0	42
B. K.	1883	12	0	9	1	12	6	28
Average	1270	18.5	7.0	7.1	4.2			48.3
SE	141.6	2.2	1.4	1.9	1.5			3.0
Smokers								
W. B.	772	1	6	1	0	5	0	56
J. E.	1925	2	0	5	5	18	16	39
A. C.	995	0	0	2	4	12	4	73
D. U.	630	10	10	4	8	3	1	54
M. W.	412	0	0	0	33	10	5	25
D. K.	1080	1	8	0	5	7	0	54
W. F.	1712	4	0	7	6	14	0	39
B. C.	710	6	5	20	0	0	1	49
A. L.	1002	0	23	14	4	1	0	32
Average	1026.4	2.6	5.8	5.9	7.2	7.8	3.8	46.8
SE	165.9	1.1	2.5	2.3	3.3	2.1	2.1	4.8

dependent of the number of pieces of luggage on a particular area at any one time.

In spite of the marked decrease in total cross-section present from peripheral to central generations, the particles disappeared in an even fashion without being held up in the more central airways (Fig. 3). This indicates that if the conveyor belt model is indeed applicable, there would appear to be a series of conveyor belts whose speeds increase from peripheral to central airways, in such a way as to prevent "particle jams" at confluence points, and, in fact, it has been pointed out that mucociliary flow varies from as little as 1 ml/min in generation 16 to 20 ml in the trachea (18, 19). Furthermore, the lack of plateau periods during which the clearance activity ceased as previously reported in patients with chronic bronchitis (4, 8), indicates the existence of a continuous mucociliary flow in the normal tracheobronchial tree. Also, visualization of the trachea when present was not interrupted so that intermittent discharge from the bronchial tree to the trachea, suggested by others (7), could not be corroborated.

In smokers, whereas patterns of deposition were similar to those of nonsmokers, patterns of clearance were markedly different. Thus, clearance curves were statistically different from those for nonsmokers and showed a delayed clearance (Fig. 6). Alterations of the clearance process in smokers are also demonstrated by the abnormally low percentage cleared during the 1st hr and by the presence of clearance at 5 and 6 hr after inhalation (Table II). These findings suggest abnormalities in the clearance of the large airways as well as prolongation of the total time of tracheobronchial clearance.

Photoscintigrams in smokers showed late retention in the trachea and larger bronchi, which suggests that the progressive increment in mucociliary flow rate from peripheral to central airways, necessary for normal clearance, is not present. By contrast (Fig. 5), when the trachea and large bronchi were visualized in nonsmokers, this occurred in the initial phase of clearance and only in the subjects with the highest initial counts,

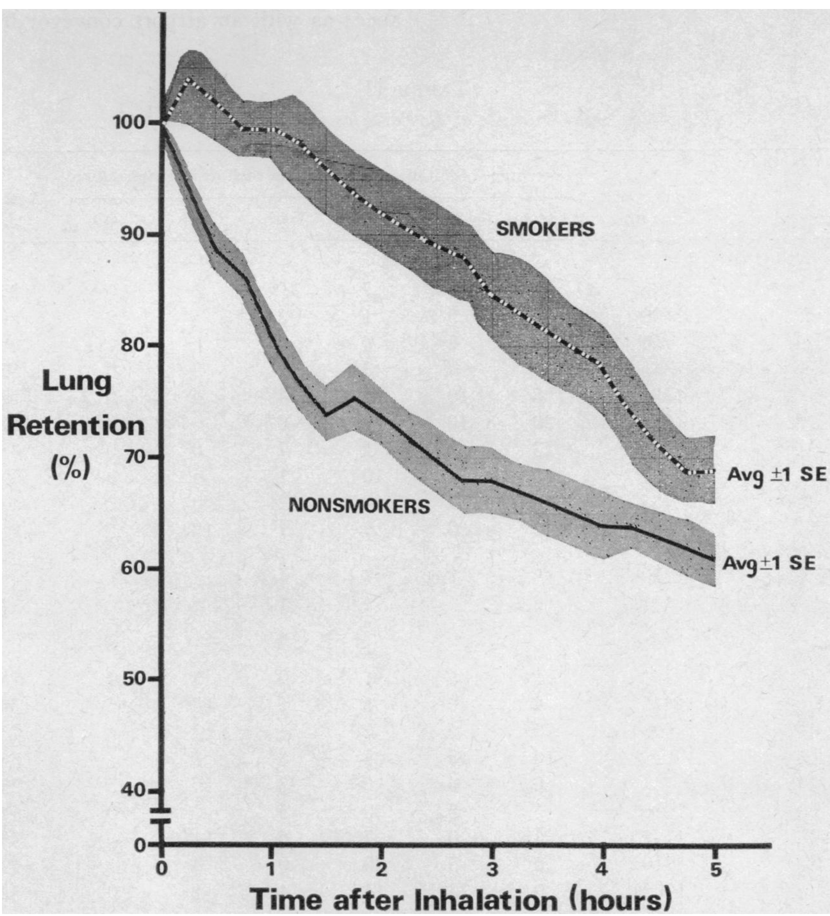

FIGURE 6 Average curves for nonsmokers (continuous line) and smokers (interrupted lines). The shaded areas represent standard errors of the means. The curves are statistically different ($P < 0.001$).

suggesting that a great number of particles were converging at the same time on large airways and not that there was an abnormal mucociliary flow rate.

Thomson and Short (9) used 5 μ particles of polystyrene labeled with ^{51}Cr to study bronchial clearance in five normal subjects, two of whom were smokers, and concluded that their data did not provide evidence for a chronic adverse effect of smoking on clearance; we believe this was due to the fact that no special attention was paid to the 1st hr after inhalation, a period in which we found important alterations, and also to the small number of subjects studied by these authors. No differences were found between smokers and nonsmokers by Luchsinger, LaGarde, and Kilfeather (6), and this may be attributed to the use of only two scintillation detectors and the very large particles (15 μ) used.

The present results agree with the findings of an abnormally long time necessary to complete 50 and 90% of bronchial clearance as reported by Albert, Lippmann, and Briscoe (10) in smokers. Our results are also compatible with experimental studies demonstrating the ciliatoxic effect of tobacco smoke (20, 21). The individual components of smoke that are deleterious for cilia and for mucus and their mode of action are not well established although there is evidence suggesting that hydrogen cyanide and acrolein have important ciliatoxic effects (22). It is possible too that enzymes important in normal ciliary activity are altered by cigarette smoking (23). In any case, the fact that abnormalities were found after periods of 2–3 hr of abstinence from smoking indicate that alterations in mucociliary activity are not easily reversible.

An alternative explanation for the delayed clearance found in smokers would be that the deposition of particles had been on more distal bronchial generations than in nonsmokers, and therefore that the particles had a longer distance to travel before being swallowed. However, as the rate of air flow, tidal volume, frequency, size, and density of particles were similar in both groups it would be necessary to postulate either the existence of impediments to air flow present only in nonsmokers or dilated bronchi in smokers; neither hypothesis is substantiated in this or any other study. Also, the pattern of deposition shown in the initial photoscintigrams and the activity retained at 24 hr were similar in smokers and nonsmokers, suggesting that significant differences in deposition were not present. Furthermore, the abnormal central retention shown in photoscintigrams late in the clearance agrees with the hypothesis of an abnormal clearance mechanism with retention of particles in the larger airways.

Finally, age may possibly change the pattern of clearance in normal subjects. However, not only were there no statistically significant differences in age between smokers and nonsmokers, but also nonsmokers (S. J. and V. L.), older than the average smoker studied, had normal clearance, and smokers (A. L., D. U., D. K., and B. C.), younger than the average nonsmoker, had abnormal clearance.

We conclude, therefore, that in smokers there are significant abnormalities in mucociliary activity which seem to be present mainly in the central airways and are reflected by an abnormal clearance of particles in the first hour after inhalation. This delay in clearance may be important in the genesis of the bronchitis frequently present in persons who smoke cigarettes.

ACKNOWLEDGMENTS

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REFERENCES

1. Proetz, A. 1939. Some preliminary experiments in the study of cigarette smoke and its effect upon the respiratory tract. *Ann. Otol. Rhinol. Laryngol.* **48:** 176.
2. Hilding, A. C. 1943. The relation of ciliary insufficiency to death from asthma and other respiratory diseases. *Ann. Otol. Rhinol. Laryngol.* **52:** 5.
3. Albert, R. E., and L. C. Arnett. 1955. Clearance of radioactive dust from the human lung. *AMA Arch. Ind. Health.* **12:** 99.
4. Toigo, A., J. J. Imarisio, H. Murmall, and M. N. Lepper. 1963. Clearance of large carbon particles from the human tracheobronchial tree. *Amer. Rev. Resp. Dis.* **87:** 487.
5. Morrow, P. E., F. R. Gibb, and K. Gazioglu. 1968. A study of particulate clearance from the human lungs. *Amer. Rev. Resp. Dis.* **96:** 1209.
6. Luchsinger, P. C., B. LaGarde, and J. E. Kilfeather. 1968. Particle clearance from the human tracheobronchial tree. *Amer. Rev. Resp. Dis.* **97:** 1046.
7. Albert, R. E., M. Lippmann, J. R. Spiegelman, A. Liuzzi, and M. Nelson. 1967. The deposition and clearance of radioactive particles in the human lung. *Arch. Environ. Health.* **14:** 10.
8. Lourenço, R. V. 1970. Distribution and clearance of aerosols. *Amer. Rev. Resp. Dis.* **101:** 460.
9. Thomson, M. L., and M. D. Short. 1969. Mucociliary function in health, chronic obstructive lung disease and asbestosis. *J. Appl. Physiol.* **26:** 535.
10. Albert, R. E., M. Lippman, and W. Briscoe. 1969. The characteristics of bronchial clearance in humans and the effects of cigarette smoking. *Arch. Environ. Health.* **18:** 738.
11. Needham, C. D., M. C. Rogan, and I. McDonald. 1954. Normal standards for lung volumes, intrapulmonary gas mixing, and maximum breathing capacity. *Thorax.* **9:** 313.
12. Kory, R. C., R. Callahan, H. G. Boren, and J. C. Syner. 1961. Veterans Administration-Army cooperative study of pulmonary function. I. Clinical spirometry in normal men. *Amer. J. Med.* **30:** 243.
13. Burrows, B., J. E. Kasik, A. H. Niden, and W. R. Barclay. 1961. Clinical usefulness of the single-breath pulmonucy diffusing capacity test. *Amer. Rev. Resp. Dis.* **84:** 789.

14. Albert, R. E., H. G. Petrow, A. S. Salam, and J. R. Spiegelman. 1964. Fabrication of monodisperse lucite and iron oxide particles with a spinning disc aerosol generator. *Health Phys.* **10**: 933.

15. Lippmann, M., and R. E. Albert. 1969. The effect of particle size on the regional deposition of inhaled aerosols in the human respiratory tract. *Amer. Ind. Hyg. Ass. J.* **30**: 257.

16. Lourenço, R. V. 1971. Proceedings of the Thirteenth Aspen Conference on Emphysema and Related Diseases. Chest. **59** (Suppl.) : 3S.

17. Newhouse, M. T., F. J. Wright, M. Dolovich, and D. L. Hopkins. 1970. Clearance of RISA aerosols in the human lung. *In* Airway Dynamics. A. Bouhuys, editor. Charles C. Thomas, Publisher, Springfield, Ill. 313.

18. Wagner, H. N., V. L. Majano, and J. K. Langan. 1965. Clearance of particulate matter from the tracheobronchial tree in patients with tuberculosis. *Nature (London).* **205**: 252.

19. Asmundsson, T., and K. H. Kilburn. 1970. Mucociliary clearance rates at various levels in dog lungs. *Amer. Rev. Resp. Dis.* **102**: 388.

20. Ballenger, J. J., F. W. Dawson, M. G. DeRuyter, and H. B. Harding. 1965. Effect of nicotine on ciliary activity in vitro. *Ann. Otol. Rhinol. Laryngol.* **74**: 303.

21. Dalhamn, T. 1966. Effect of cigarette smoke on ciliary activity. *Amer. Rev. Resp. Dis.* **93**: 108.

22. Wynder, E. L., D. A. Goodman, and D. Hoffman. 1965. Ciliatoxic components in cigarette smoke. III. In vitro comparison of different smoke components. *Cancer.* **18**: 1652.

23. Cress, H. R., A. Spock, and D. C. Heatherington. 1965. The localization of succinic dehydrogenase, cytochrome oxidase and adenosine triphosphatase in ciliated respiratory epithelium. *J. Histochem. Cytochem.* **13**: 677.