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Deposition, retention, and clearance of inhaled particles*

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ABSTRACT The relation between the concentrations and characteristics of air contaminants in the work place and the resultant toxic doses and potential hazards after their inhalation depends greatly on their patterns of deposition and the rates and pathways for their clearance from the deposition sites. The distribution of the deposition sites of inhaled particles is strongly dependent on their aerodynamic diameters. For normal man, inhaled non-hygroscopic particles $\gtrsim 2$ μm that deposit in the conducting airways by impaction are concentrated on to a small fraction of the surface. Cigarette smoking and bronchitis produce a proximal shift in the deposition pattern. The major factor affecting the deposition of smaller particles is their transfer from tidal to reserve air.

For particles soluble in respiratory tract fluid, systemic uptake may be relatively complete for all deposition patterns, and there may be local toxic or irritant effects or both. On the other hand, slowly soluble particles depositing in the conducting airways are carried on the surface to the glottis and are swallowed within one day. Mucociliary transport rates are highly variable, both along the ciliated airways of a given individual and between individuals. The changes in clearance rates produced by drugs, cigarette smoke, and other environmental pollutants can greatly increase or decrease these rates. Particles deposited in non-ciliated airways have large surface-to-volume ratios, and clearance by dissolution can occur for materials generally considered insoluble. They may also be cleared as free particles either by passive transport along surface liquids or, after phagocytosis, by transport within alveolar macrophages. If the particles penetrate the epithelium, either bare or within macrophages, they may be sequestered within cells or enter the lymphatic circulation and be carried to pleural, hilar, and more distant lymph nodes. Non-toxic insoluble particles are cleared from the alveolar region in a series of temporal phases. The earliest, lasting several weeks, appears to include the clearance of phagocytosed particles via the bronchial tree. The terminal phases appear to be related to solubility at interstitial sites. While the mechanisms and dynamics of particle deposition and clearance are reasonably well established in broad outline, reliable quantitative data are lacking in many specific areas. More information is needed on: (1) normal behaviour, (2) the extent of the reserve capacity of the system to cope with occupational exposures, and (3) the role of compensatory changes in airway sizes and in secretory and transport rates in providing protection against occupational exposures, and in relation to the development and progression of dysfunction and disease.

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The major regions of the respiratory tract differ considerably in structure, size, function, and sensitivity or reactivity to deposited particles. Some also have different mechanisms for particle elimination. Thus a complete determination of dose from an inhaled aerosol depends on (1) the regional deposition, (2) the retention times at the deposition sites and along the elimination pathways, and (3) the physical, chemical, and biological properties of the particles.

Particles that contain liquid water and are hygroscopic can change in size as they are carried through the warm and humid atmosphere in the conducting airways. Dissolved materials within deposited particles can rapidly diffuse within and through the fluid lining of the airways. On the other hand, insoluble particles that deposit within the conducting airways undergo passive transport determined by the motion of the mucous layer. Thus the behaviour of insoluble particles during the bronchial clearance phase may be discussed in a more general way than that of particles that are rapidly soluble or highly irritating. For soluble particles and for insoluble particles that deposit within the non-ciliated alveolar zone, each different aerosol requires individual consideration on the basis of its chemical composition.

Functional zones for particle deposition

The respiratory tract (fig 1) may be divided into zones on the basis that the insoluble particles that deposit in each zone contact or affect different cell populations or have substantially different retention times and different clearance pathways or both. Each zone includes one or more anatomical regions.

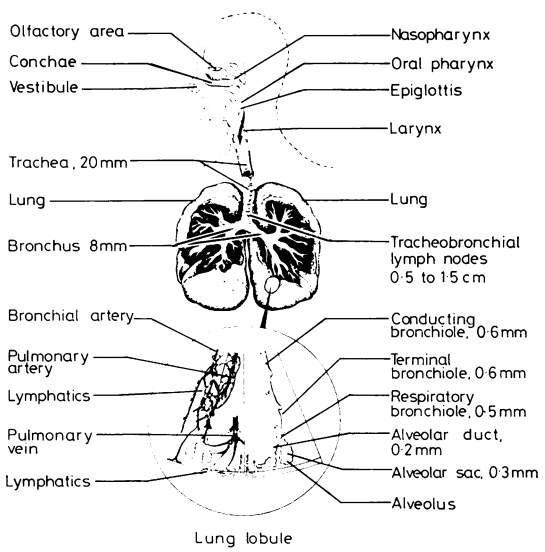

Fig 1 *Structure of respiratory tract. (Courtesy National Academy of Sciences, National Research Council.)*

ANTERIOR NARES

Particles deposited in the unciliated anterior portion of the nose remain at the deposition sites for a variable and usually indeterminate period until they are removed mechanically by nose wiping, blowing, sneezing, etc. The effect of particle solubility on retention in this zone is not known.

CILIATED NASAL PASSAGES

After leaving the nares, the inspired air passes through a web of nasal hairs and flows around the turbinates. It is warmed, moistened, and partially depleted of particles with aerodynamic diameters $> 1\ \mu m$ by impaction on the nasal hairs and at bends in the air path, and by sedimentation. Particles $< 0{\cdot}1\ \mu m$ can deposit in this zone by diffusion. The surfaces are covered by mucus, most of which is propelled toward the pharynx by the beating of the cilia, carrying with it deposited insoluble particles. Soluble particles may be dissolved in the mucus. Some mucus moves toward the anterior nares, carrying inhaled whole or dissolved particles into the zone of intermittent mechanical clearance.

NASOPHARYNX, ORAL PASSAGES, LARYNX (NON-CILIATED LARGE AIRWAYS)

Particles inhaled through the nose and deposited in the nasopharynx or particles inhaled through the mouth and deposited there or in the oropharynx are generally swallowed. Particles inhaled by either route may also deposit on the larynx and be carried rapidly to the oesophagus in or on the mucus coming up from the trachea.

The residence times for particles in these zones may be very short, but local deposition may be important. Concentration build-up on some of these surfaces can be high and may exceed the capacity for clearance; perhaps accounting for nasal cancers in furniture workers[1-4] and for laryngeal cancers in cigarette smokers[5] (T Hirayama in report presented at the America Cancer Society's Fourteenth Science Writers' Seminar, Clearwater Beach, Fla).

TRACHEOBRONCHIAL TREE

The tracheobronchial or conducting airways have the appearance of an inverted tree, with the trachea analogous to the trunk and subdividing bronchi to the limbs. The airway diameter decreases distally, but because of the increasing number of tubes the total cross section increases and the air velocity decreases. In the larger airways particles too massive

to follow the bends in the air path are deposited by impaction. At the low velocities in the smaller airways particles deposit by sedimentation and diffusion. Ciliated and secretory cells are found at all levels. Inert non-soluble particles deposited on normal ciliated airways are cleared within one day via the larynx on the moving mucus.[6] Soluble particles are cleared much faster, presumably via bronchial blood flow.[7]

ALVEOLAR ZONE

Gas exchange takes place beyond the ciliated airways. The epithelium is very thin, and soluble particles are believed to enter the pulmonary blood within minutes. Insoluble particles deposited there by sedimentation and diffusion are removed very slowly, with clearance half-times measured in days, months, or years. The mechanisms for clearing insoluble particles from the alveolar zone are only partly understood, and their relative importance is a matter of some debate.

Factors affecting particle deposition

Particles deposit in the various regions of the respiratory tract by varying physical mechanisms. Deposition efficiency in each region depends on the aerodynamic properties of the particles, the anatomy of the airways, and the geometric and temporal patterns of flow.

DEPOSITION MECHANISMS

There are five mechanisms by which significant particle deposition can occur within the respiratory tract—interception, impaction, sedimentation, diffusion, and electrostatic precipitation. In most cases, however, only impaction, sedimentation, and diffusion will be important.

Interception is usually significant only for fibrous particles. It occurs when the trajectory of a particle brings it close enough to a surface so that an edge contacts the surface; thus the particle size must be a significant fraction of the airway diameter. Some fibres 200 μm long have been observed in human lung samples.[8] Straight fibres, such as amphibole asbestos, are more likely to penetrate to the alveoli than similar sized but curly chrysotile asbestos, because the straight fibres assume orientations more parallel to the flow streamlines.

The inhaled air follows a tortuous path through the nose or mouth and branching airways in the lung. Each time the air changes direction, the momentum of particles tends to keep them on their pre-established trajectories, which can cause them to impact on airway surfaces. The most likely deposition sites are at or near the carinas of the large airway bifurcations.

Gravitational sedimentation is an important mechanism for deposition in the smaller bronchi, the bronchioles, and the alveolar spaces, where the airways are small and the air velocity is low.

Sedimentation becomes less effective than diffusion when the terminal settling velocity of the particles falls below $\sim$ 0·001 cm/s, which for unit density spheres is equivalent to a diameter of 0·5 μm.

Submicron particles in air undergo a random motion caused by the impact of gas molecules. This Brownian motion increases with decreasing particle size and becomes an effective mechanism for particle deposition in the lung as the root-mean-square displacement approaches the size of the air spaces.

Diffusional deposition is important in small airways and alveoli and at airway bifurcations for particle sizes below $\sim$ 0·5 μm. For radon and thoron daughters, where the particle size is molecular, diffusional deposition efficiency can be high in the head and in large airways such as the trachea.

Particles with high electric mobility can have an enhanced respiratory tract deposition even though no external field is applied across the chest. Deposition results from the image charges induced on the surface of the airways by the charged particles. Test aerosols from evaporation of aqueous droplets can have substantial mobilities, and the results of some experimental deposition studies using such aerosols without charge neutralisation are accordingly suspect. Freshly fractured mineral dust particles may be highly charged. Most aerosols have lower charge levels, however, and the deposition due to charge is usually small in comparison to deposition by the preceding mechanisms.

AEROSOL FACTORS

There are several ways of expressing particle size. When measured by one unit and expressed in terms of another or equivalent size, the basis for the conversion must be clearly established. Non-spherical particles are often characterised in terms of equivalent spheres—for example, on the basis of equal volumes, equal masses, or aerodynamic drag. A unit of increasingly common use is called aerodynamic diameter (D), which incorporates both particle density and drag.

Aerodynamic diameter is the most appropriate unit in terms of particle deposition by impaction and sedimentation. Diffusional displacement, which is the dominant mechanism for particles $< 0{\cdot}5$ μm, depends only on particle size and not on density or shape. Interception also depends on the linear dimensions of the particle, including its shape, since aerodynamic drag can affect orientation within the airway.

The conversion of linear or projected area microscopic measurements of non-spherical particles to aerodynamic diameters requires assumptions about the relation between projected area and volume, about density, and about aerodynamic shape factors. Such conversions can sometimes be made accurately, but in many cases have been made without adequate corrections. An alternative approach is to measure aerodynamic size directly, using an aerosol spectrometer.[9–11]

A complicating factor for water-soluble particles is the change in size that occurs in humid atmospheres. Furthermore, dry aerosols of materials, such as sodium chloride, sulphuric acid, and glycerol, will take up water vapour and grow in size within the warm and nearly saturated atmosphere in the lungs.[12 13] Such changes in size may cause significant changes in deposition pattern and efficiency.

RESPIRATORY AND FLOW FACTORS

Increasing air velocity increases impaction deposition but decreases sedimentation and diffusion by decreasing residence time. The flow is cyclical and reverses many times a minute. At its peak it may be turbulent in the trachea, but the Reynolds number decreases with increasing lung depth, so that in the smaller conducting airways it is always laminar and in the alveolar region viscous.[14]

Since the flow is laminar in most of the anatomical dead space the central core velocity is almost twice the average velocity. Thus even in very shallow breathing a substantial fraction of the inhaled volume penetrates beyond the anatomical dead space, and particles with appreciable sedimentation rates—for instance, size $> 2\ \mu$m—or large diffusional displacements—for instance, size $< 0{\cdot}1\ \mu$m—can deposit efficiently in peripheral airways.

The tidal volume is an important respiratory factor. The air inhaled at the start of each breath goes deeper into the lung and remains there longer than the air inhaled later in the breath. It follows that the deeper the air goes and the longer it stays the greater its depletion of inhaled particles. Thus for quiescent breathing, when the air velocity is low, mixing is minimal, and the tidal volume is only two to three times the dead space volume, a large proportion of the inhaled particles can be exhaled. Conversely, for heavy exertion when the larger volumes are inhaled at higher velocities, both impaction in the large airways and sedimentation and diffusion in the smaller airways and alveoli will be greater.

ANATOMICAL FACTORS

Individual variations in airway anatomy affect particle deposition in several ways: (1) the diameter of the airway influences the displacement required by the particle before it contacts the airway surface; (2) the cross section of the airway determines the flow velocity for a given volumetric flowrate; and (3) the variations in diameter and branching patterns along the bronchial tree affect the mixing characteristics between the tidal and reserve air in the lungs. For particles with aerodynamic diameters below $\sim 2\ \mu$m, convective mixing can be the most important factor determining deposition efficiency.

There are also significant individual differences in respiratory tract anatomy. For example, the average alveolar zone air space dimension has a substantial coefficient of variation when measured either post-mortem on lung sections or in vivo by aerosol persistence during breath holding. In the former, Matsuba and Thurlbeck[15] reported a mean size and variation of $0{\cdot}678$ mm $\pm$ $0{\cdot}236$. In the latter, Lapp *et al*,[16] found values of $0{\cdot}535$ mm $\pm$ $0{\cdot}211$.

PHYSIOLOGICAL FACTORS

The surface of the mucous layer defines the effective diameters of the conducting airways for airflow. In normal subjects the mucous layer on the larger conductive airways is believed to be only about $5\ \mu$m thick[17] and decreases with airway size. In terminal bronchioles it may be only $0{\cdot}1\ \mu$m thick.[18] Hence, the reduction in air path cross section by the mucus is negligible. On the other hand, in bronchitics, the mucous layer may be much thicker and in some places may accumulate and partially or completely occlude the airway. Air flowing through partially occluded airways will form jets, which will probably cause increased small airway particle deposition by impaction and turbulent diffusion.

ENVIRONMENTAL FACTORS

There is relatively little information on the effects of temperature and humidity on particle deposition, although ambient humidity can greatly affect the size of many pollutant particles and thereby affect their deposition.

EFFECTS OF OTHER GASES AND AEROSOLS

Inhaled irritants can affect the fate and toxicity of inhaled particles by altering airway calibre, respiratory function, clearance function or the function, survival, and distribution of the cells that line the airways, or all. Any reduction in airway cross section in the larger bronchial airways results in increased flow velocities and should, therefore, increase particle deposition by impaction. Increased bronchial deposition of inhaled particles was observed in tests in which two normal young men were exposed to sulphur dioxide. A seven-minute exposure to 13 ppm decreased the alveolar zone

deposition of 4·6 μm aerodynamic diameter particles from 10% to 2% and produced an appreciable proximal shift in the bronchial deposition pattern. A six-minute exposure to 12 ppm in a second subject decreased alveolar deposition of 5·9 μm particles from 18% to 4%. Tests on two other subjects at 5 and 9 ppm did not produce any significant shift in regional deposition.[19] Tracheobronchial particle deposition is significantly greater in cigarette smokers than in non-smokers,[20-22] presumably due to the bronchoconstrictive properties of cigarette smoke.

EFFECTS OF CHRONIC LUNG DISEASE

While some normal cigarette smokers have increased bronchial deposition, the increase is relatively small compared with that seen in individuals with clinically defined chronic bronchitis.[20 23 24] Greatly increased tracheobronchial particle deposition has also been seen in some asymptomatic asthmatics.[20]

Love *et al*[25] found no change in total deposition of 1 μm particles associated with simple pneumoconiosis. In a subsequent report, Love and Muir[26] found that total deposition correlated significantly with the degree of airway obstruction, but no correlation occurred between the presence of simple pneumoconiosis and total deposition.

Heppleston[27] investigated the distribution of inhaled haematite particles in the lungs of rats which had pneumoconiotic lesions from prior exposures to coal or silica. Compared with normal rats the haematite was deposited more distally in both groups of pneumoconiotic rats.

Hankinson *et al*[28] measured aerosol persistence during breath holding in 127 coal miners. Of these, 35 had radiographic category 0 (no) pneumoconiosis, 34 type q (micronodular), and 58 type p (pinhead) pneumoconiosis There were no significant differences among the three groups with regard to mean height or respiratory function. As a group, type q had more advanced radiographic changes than type p. There were no significant differences, however, in aerosol persistence between the type q group and the category 0 miners or the non-miner controls previously studied.[16] The miners with type p opacities had significantly larger mean alveolar zone airspace sizes than did any of the other groups. They also had smaller conducting airway sizes than the other groups.

Experimental deposition data

TOTAL DEPOSITION

Relatively few attempts have been made to measure regional particle deposition in man. A much larger number of studies have explored total deposition. For particles between ~ 0·1 and 2 μm aerodynamic diameter, deposition in the conducting airways is generally very small by comparison with deposition in the alveolar regions, and thus total deposition approaches alveolar deposition. Total deposition as a function of particle size and respiratory parameters has been measured experimentally by numerous investigators. Many previous reviews on deposition have called attention to the very large difference in the reported results.[29-33]

Much of the discrepancy may be attributed to uncontrolled experimental variables and poor experimental technique. The major sources of error have been described by Davies.[14] Figure 2 shows data from studies performed with good techniques and precision. All were done with mouth breathing at respiration frequencies of from 12 to 16. Tidal volumes varied from 0·5 to 1·5 l. All appear to show the same trend with a minimum of deposition at ~ 0·5 μm diameter.

The data of Heyder *et al*[42 43] appear to represent deposition minima for normal men for several reasons. Their test protocols were precisely controlled; there were no electrical charges on their particles; and their volunteer subjects had less deposition than did other individuals subsequently tested under the same conditions.[44] The data of Landahl *et al*,[34 35] Altshuler *et al*,[36] Giacomelli-Maltoni *et al*,[37] and Martens and Jacobi,[38] which are higher, agree quite well with each other. In these studies there were respiratory pauses, and the peak flows were higher.

The deposition data in fig 2 were based on the difference between inhaled and exhaled particle concentration, except for the data of Lippmann[31] and Foord *et al*,[39] which are based on external in vivo measurements of γ-tagged particle retention. In further studies using γ-tagged test aerosols Chan and Lippmann[45] and Stahlhofen *et al*[46] obtained similar results (fig 3).

HEAD DEPOSITION

The nasal route is a more efficient particle filter than the oral, especially at low and moderate flowrates, thus, persistent mouth breathers deposit more particles in their lungs than those who breathe entirely through the nose. During exertion, the flow resistance of the nasal passages causes a shift to mouth breathing in almost all people.

Experimental data relating to deposition in the head during mouth and nose breathing are summarised and reviewed by Lippmann.[31] The recent results of Stahlhofen *et al*[46] for mouth breathing agree well with earlier data.

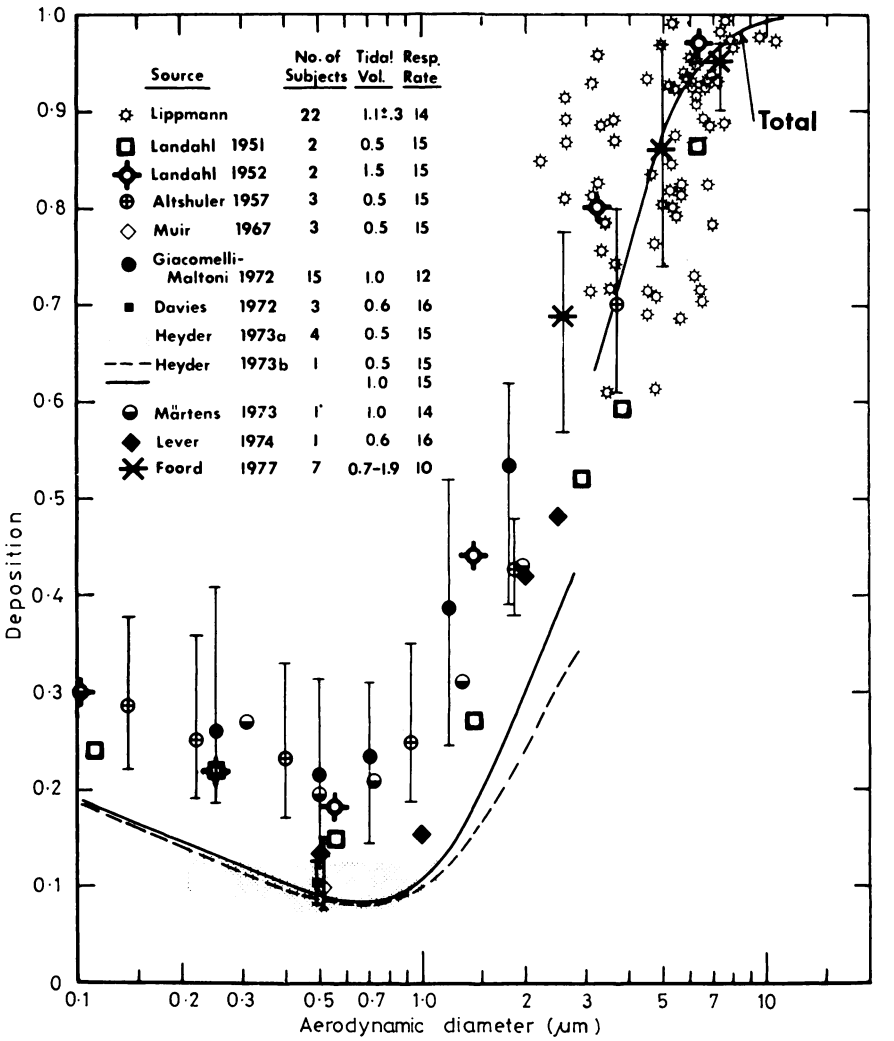

Fig 2 *Total respiratory tract deposition during mouthpiece inhalations as a function of aerodynamic diameter in μm, except below 0·5 μm, where deposition is plotted v linear diameter. Data of Lippmann[29] are plotted as individual tests, with eye-fit average line. Other data on multiple subjects are shown with average and range of individual tests. Monodisperse test aerosols used were Fe_3O_3[31] triphenyl phosphate,[34–36] carnuba wax,[37] polystyrene latex,[38 39] and di-2-ethyl-hexyl-sebacate.*[14 39–44]

DEPOSITION IN THE TRACHEOBRONCHIAL ZONE

The only published in-vivo measurements of human tracheobronchial deposition are those of Lippmann and Albert,[50] Lippmann *et al*,[20] Lippmann,[31] Foord *et al*,[39] Stahlhofen *et al*[46] and Chan and Lippmann[45] (figs 4 and 5).Tracheobronchial deposition for a given particle size varies greatly from subject to subject among both non-smokers, cigarette smokers, and patients with lung disease. Average tracheobronchial deposition is slightly raised in smokers and greatly raised in the patients. Among normal subjects and non-bronchitic smokers, however, each individual has a characteristic and reproducible relationship of particle size to deposition. Tracheobronchial deposition includes both deposition by impaction in the

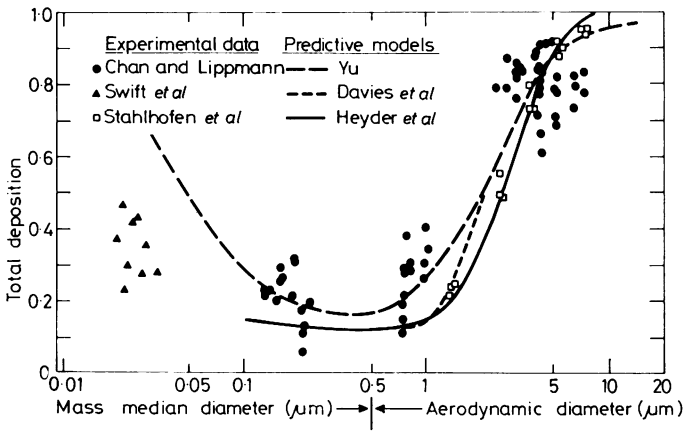

Fig 3 *Total respiratory tract deposition as a function of particle size. Experimental data are from γ-tagged aerosol inhalation studies by Swift et al (presented in part at the 1977 American Independent Hygiene Conference, New Orleans, 26 May 1977), Chan and Lippmann,[45] and Stahlhofen et al.[46] The predictive models are those of Yu,[47] Davies et al,[48] and Heyder et al.[49]*

larger airways and deposition by sedimentation in the smaller airways. Impaction deposition predominates for large particles (D > 3 μm) and high flowrates (F > ~ 20 lpm), while sedimentation deposition becomes a larger fraction of a diminishing tracheobronchial component for smaller particles and lower flows.

For deposition within the tracheobronchial zone, the pattern of deposition within hollow airway casts made from normal human lungs shows that the airway bifurcations accumulate a disproportionate share of the tracheobronchial deposits.[51 52] Furthermore, there appears to be a close correspondence between the density of the surface deposition on the bifurcation regions and the incidence of primary cancer sites. The largest number of human lung cancers are found in lobar bronchi. Among the lobar bronchi, the largest number are found at the right upper bronchus and the lowest in the right middle bronchus. Figure 6 shows cast deposition data for the lobar bronchi for various particle sizes and flow-rates. While the absolute amounts of deposition vary considerably with particle size and flow-rate, the relative amounts on the various lobar bronchi remain relatively constant and appear to be closely associated with reported cancer incidence.

DEPOSITION IN THE ALVEOLAR ZONE

Figure 7 shows alveolar deposition values obtained in mouth-breathing inhalation tests on non-smoking normal subjects. These data are based on external measurements of retention of γ-tagged particles after the completion of bronchial clearance. The data of Chan and Lippmann[45] and Stahlhofen *et al*,[46] both appear to be consistent with the earlier data of Lippmann and Altshuler.[19]

Figure 8 shows an estimate of the alveolar deposition that could be expected when the aerosol is inhaled via the nose. It is based on the difference in head retention during nose breathing and mouth breathing from the analysis of Lippmann.[31] For mouth breathing the size for maximum deposition is ~ 3 μm, and ~ 0·5 of the inhaled aerosol at this size deposits in this region. For nose breathing, there is a much less pronounced maximum of ~ 25% at 2·5 μm, with a nearly constant alveolar deposition averaging about 20% for all sizes between 0·1 and 4 μm.

The alveolar deposition curves of Lippmann and Altshuler[19] in fig 8 are shown with the sampler acceptance criteria of the British Medical Research Council (MRC)[53] and of the American Conference of Governmental Industrial Hygienists,[54] which define the cut-off characteristics of the precollectors preceding respirable dust samplers. Both provide reasonable approximations of the cut-off characteristics of the human conducting airways, at least of non-smoking normal subjects. Figure 8 also includes the alveolar deposition calculated on the basis of the Task Group Model,[33] which, like most predictive models, departs significantly from the deposition observed in reliable experimental studies.

Predictive deposition models

The earliest mathematical models for predicting the regional deposition of aerosols were those of Findeisen,[55] Landahl,[56 57] and Beeckmans.[58] Findeisen's simplified anatomy, with nine sequential regions from the trachea to the alveoli, and his impaction and sedimentation deposition equations were used in the Task Group's model.[33] For diffusional deposition, the Task Group used the equations of Gormley and Kennedy,[59] and for head deposition they assumed entry through the nose with a deposition efficiency given by the empirical

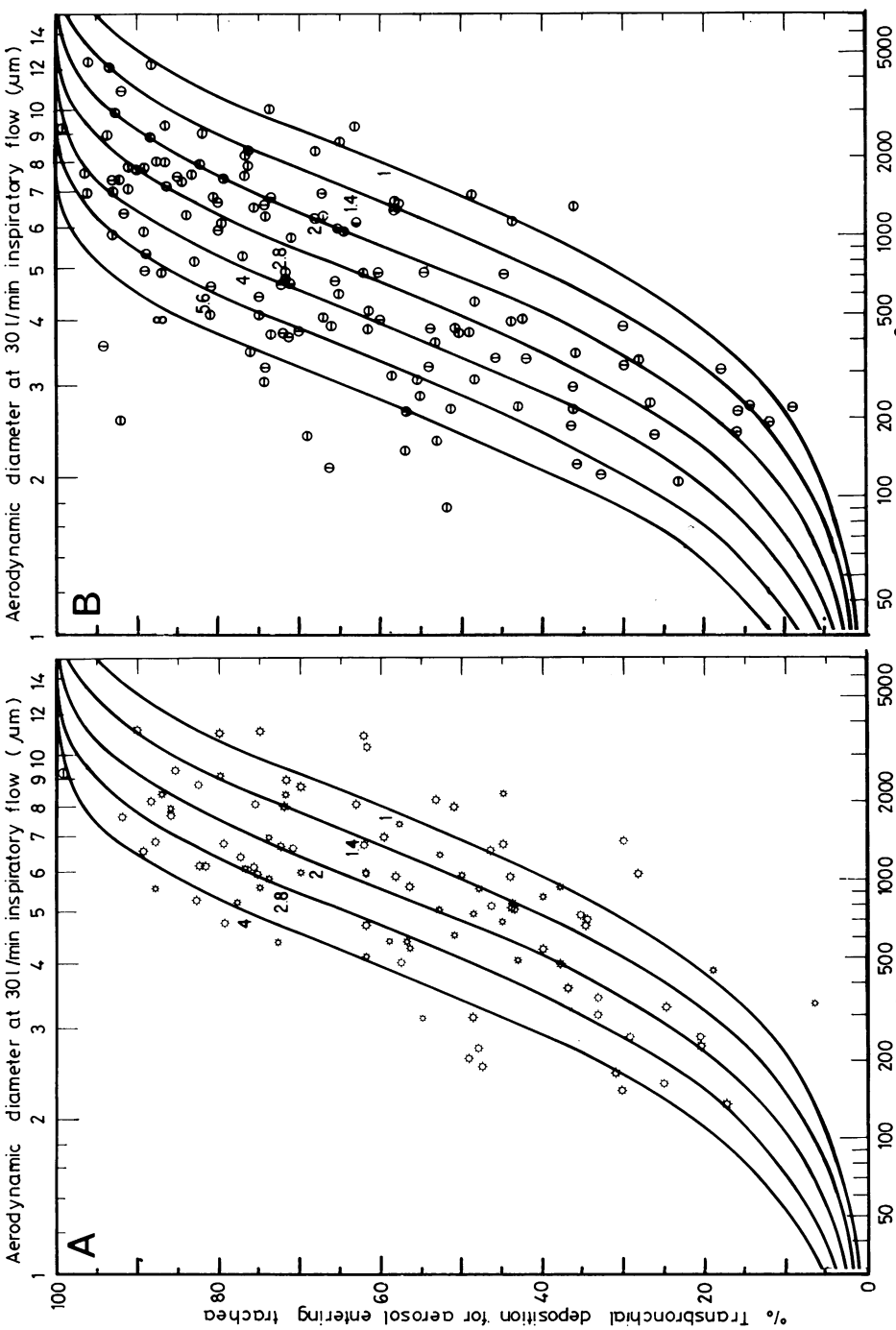

Fig 4 *Deposition in ciliated tracheobronchial region during mouthpiece breathing, in % of aerosol entering trachea. Panel A shows data for non-smoking normal men, while panel B contains data for cigarette smokers. Curves represent change in tracheobronchial deposition as a function of D^2F for different values of characteristic airway dimension parameter developed by Palmes and Lippmann.[22] Comparison of the two panels shows that many cigarette smokers have increased tracheobronchial deposition. Non-smoker's data are from same tests for which total respiratory tract depositions are shown in fig 2.*

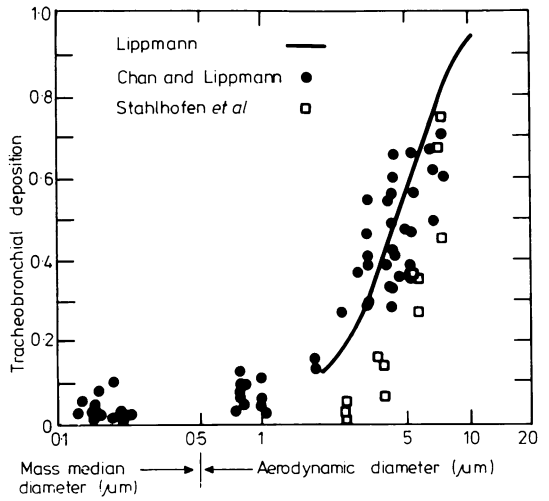

Fig 5 *Experimental tracheobronchial deposition data for γ-tagged aerosol inhalation studies. Data points are those of Chan and Lippmann*[45] *and Stahlhofen et al.*[47] *Solid line represents median of earlier experimental study of Lippmann.*[31]

equation of Pattle.[60] In comparison between the various predictions, Landahl's model comes closest but overestimates alveolar deposition for particles with aerodynamic diameters larger than 3·5 μm.

The Task Group's model[33] was adopted by ICRP Committee II in 1973, with numerical changes in some clearance constants. The Task Group report has been widely quoted and used within the health physics field. One of the significant conclusions of the study was that regional deposition within the respiratory tract may be estimated using a single aerosol measurement—the mass median diameter. For a tidal volume of 1450 cm^3, there were relatively small differences in estimated deposition over a very wide range of geometric standard deviations ($1{\cdot}2 < \sigma_g < 4{\cdot}5$).

Among the predictive models developed in recent years, the theoretical model of Yu[47] and the empirical models of Heyder *et al*[49] and Davies *et al*[48] provide reasonably reliable estimates of particle deposition efficiencies in some normal men. None of the available models, however, gives any measure of the very large variability in deposition efficiencies among normal subjects. The effect of

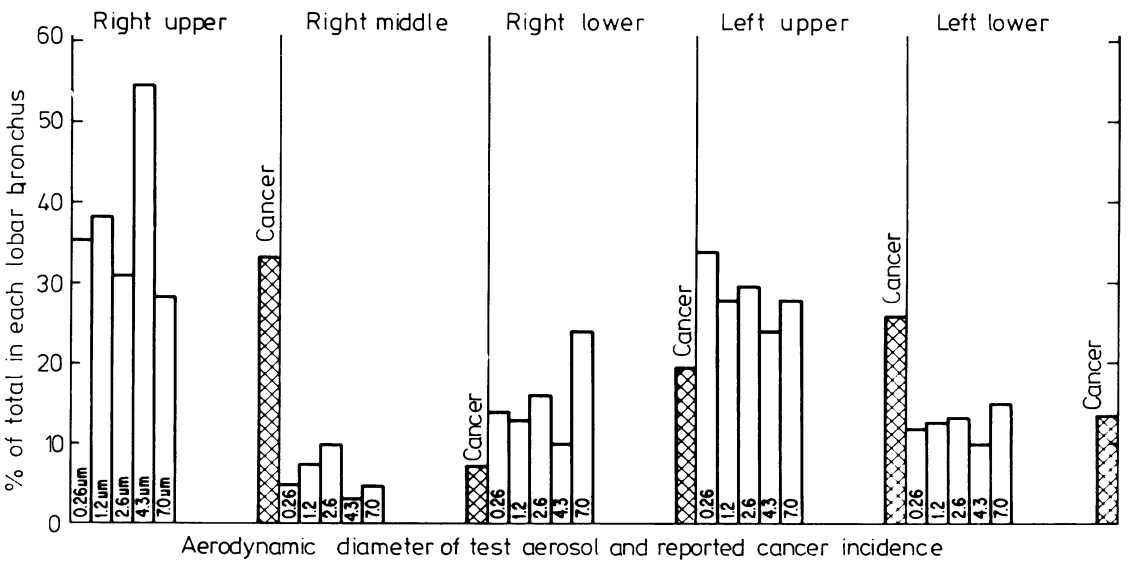

Fig 6 *Percentage of total particle deposition within five lobar bronchi of cast that occurs within each lobar bronchus, compared with the reported percentage of total lobar bronchial carcinomas that originate within each lobar bronchus, at a flow rate of 30 l/min. Data on cancer sites are from Schlesinger and Lippmann.*[51]

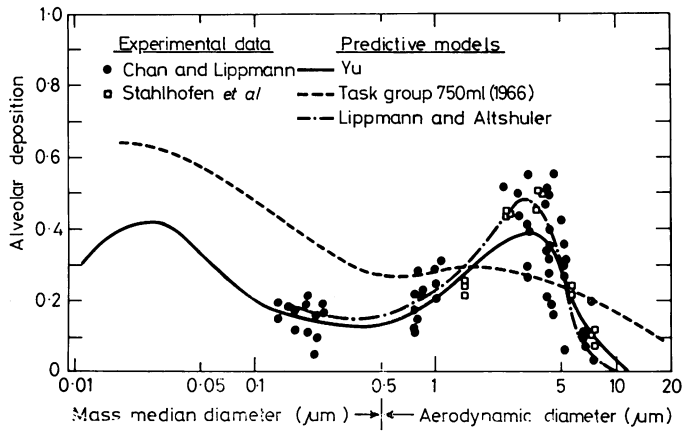

Fig 7 *Deposition in non-ciliated alveolar region, in % of aerosol entering mouthpiece, as a function of aerodynamic diameter, except below 0·5 μm, where linear diameter was used. Data points are for Fe_2O_3 aerosol tests of Chan and Lippmann[45] and Stahlhofen et al.[46] Dot-dash line is an eye-fit through median best estimates of Lippmann and Altshuler.[19] Solid line shows predictive theoretical model of Yu.[47]*

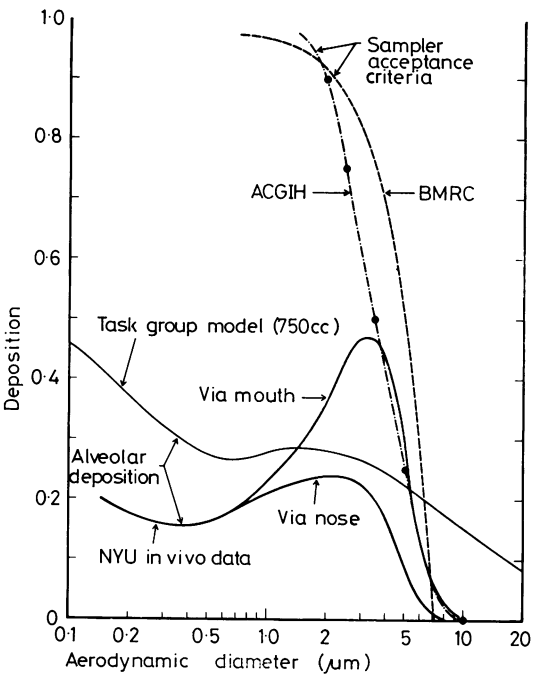

Fig 8 *Comparison of sampler acceptance curves of BMRC and ACGIH with alveolar deposition according to Task Group[33] and from the experimental New York University deposition data of Lippmann and Altshuler.[19] Lower curve is an estimate of alveolar deposition during nose breathing, and is based on difference in efficiency in head deposition from data of Lippmann.[31]*

intersubject variability on total respiratory tract deposition is illustrated in fig 9. Here, Palmes and Lippmann[22] have used the experimental data of Giacomelli-Maltoni *et al*[37] to construct a family of curves showing deposition by percentiles of the overall population. It can be seen that, within this particle size range, deposition for the top 2% of the population is from 34% to 54% higher than for the median subject. Other variations in deposition are produced by cigarette smoke (fig 4) and lung disease.[20 61] The measurement of deposition has advanced significantly in recent years, however, and considerable effort is under way to improve theoretical understanding and predictive models.

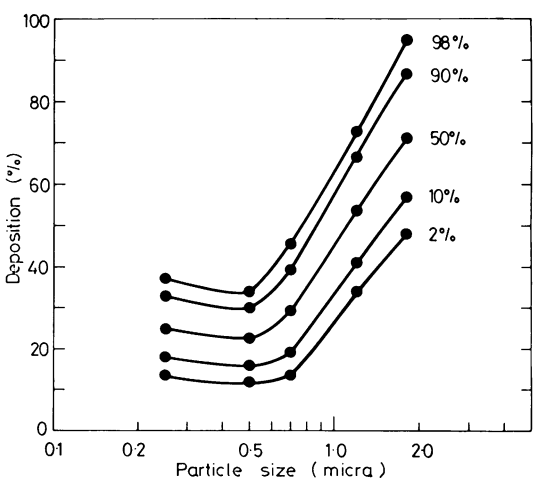

Fig 9 *Range of expected total respiratory tract deposition values based on experimental data of Giacomelli-Maltoni et al.[37] Each curve represents indicated percentile of overall population. (From Palmes and Lippmann,[22] courtesy Pergamon Press.)*

Particle retention

Particle retention is a time-dependent variable equal to the difference between the amount of aerosol deposited and the amount cleared. For a given individual rates of clearance within the respiratory tract vary greatly from region to region. This variation was a major basis for the characterisation of functional zones described earlier. In two of these zones—that is, the ciliated nasal passages and the tracheobronchial tree—clearance in normal individuals is completed in less than one day. In the alveolar zone clearance proceeds by slower processes, most of which vary considerably with the composition of the particles.

Clearance of particles from the conducting airways

Particles that deposit in the airways may be cleared by several mechanisms. The most important for insoluble particles is mucociliary clearance. Soluble particulates, depending on their physicochemical properties, may either be incorporated into the mucus, be taken up by the airway epithelium, or pass through it to be cleared by the bronchial and pulmonary circulations. It has been suggested that some insoluble particles may penetrate the mucus and enter epithelial cells.[62] Conversely, it has been postulated that particles from interstitial spaces and lymphatics may enter the airway lumen and be subsequently removed by mucociliary activity.[63 64] The clinical aspects of mucociliary transport have recently been described by Wanner.[65] This review will concentrate on the role of mucociliary transport in the normal lung as a defence mechanism through its clearance of inhaled particles.

MORPHOLOGICAL DESCRIPTION OF THE AIRWAYS

The tracheobronchial airways extend from the larynx to the terminal ciliated bronchioles, the airways where proximal mucociliary transport begins. The model of Horsfield *et al*[66] has 233 920 terminal ciliated bronchioles, each 0·4 mm in diameter and 0·48 mm long. They have a cumulative circumference of 30 000 cm, compared with the 5 cm of the trachea. These converge in a symmetrical fashion for six branching orders into airways 0·76 mm in diameter with a cumulative circumference of 1480 cm. The total surface area of these airways is 3810 cm^2. The epithelium at this level consists of ciliated cells dispersed among Clara cells, brush cells, epithelial serous cells, K cells, globule leukocytes, and sparse basal cells.[67] The cilia are shorter and sparser here than in the large airways.[68] The airways at this level are lined with a uniform proteinaceous layer that is only 0·1 μm thick in the rabbit,[18] and contains a surfactant-like material that is important in maintaining small airway patency.[69] Transport of particles proximally in this region is probably due to both ciliary beating and the energy provided by the surface tension differences in the alveoli (2-10 dynes/cm^2) and airways ($\sim$70 dynes/cm^2). Transport rates in these airways have not been measured but have been calculated to be from 10 to 200 μm/min by Yeates and Aspin[70] and 100-600 μm/min by Morrow *et al*.[71]

These small airways may be at special risk for several reasons. The most rapid change in circumference takes place in these airways, decreasing by a factor of 20 within the first 7 mm of cumulative airway length. Thus a small increase in the volumes of cellular secretions or fluid transudation could lead to a rapid increase in the thickness of the fluid layer. Also, the airway fluid lining may be much more permeable to inhaled particles and vapours than the more continuous, thicker, and more viscous mucous blanket of the larger airways. Additionally, the retention times for particles deposited in these airways are greater.

The next zone proximally contains airways between 0·76 and 3·1 mm. This region has asymmetrical branching and a cumulative surface area of 1190 cm^2. In this region the total circumference decreases to 22 cm. The ciliated epithelium becomes continuous but is still only 20-30 μm deep and has few basal cells. The ciliated cells are more numerous and occupy about half of the surface; Clara cells are sparser, and goblet cells, which secrete a relatively viscous mucus, are more numerous. The cell turnover time has been estimated to be 59 days in small bronchi.[72] These bronchioles are covered with a continuous mucous sheath as shown by Ebert and Terracio[73] and Sturgess.[74] Controversy on this issue remains, however.[75] The continuous blanket of viscous mucus consists of loosely intertwined glycoprotein strands and is transported on the tips of the cilia. The cilia beat in a less viscous fluid, which is thought to consist of serum transudate and secretions from Clara cells. Its depth may be controlled by an active chloride pump in the epithelium layer. The transport rates in this region have been calculated to be 0·2-1·3 mm/min.[70]

The ciliated epithelium from the subsegmental bronchi proximally is fully developed pseudostratified columnar, and is 50-70 μm thick.[76] At this level, basal cells are numerous while at the surface the ciliated cells form a dense mat-like appearance. There are no Clara cells. The turnover rate of this epithelium is probably about 18 days.[72] Mucus is produced by submucosal glands that lie in juxtaposition to the cartilaginous plates and rings

of these airways. The ducts from these glands perforate the epithelium, with a surface density of about one per square millimeter. It has been postulated that most of the mucus is secreted by these glands, as they contain 40 times the volume of the goblet cells.[77] The mucus in these airways forms a continuous sheet about 5 μm thick overlying the tips of the cilia and is transported at about 1-5 mm/min.[78 79]

REACTIONS TO INHALED TOXICANTS

The distribution of cell types in the airways changes with insults from inhaled noxious agents and in chronic obstructive airways disease. Hypertrophy of mucous glands and hyperplasia of goblet cells have been observed in people with chronic bronchitis. The hypertrophy of the mucous glands occurs at the expense of lumen size. Rats have shown hyperplasia of goblet cells after exposure to irritants such as cigarette smoke.[80] This increase in mucus secretory apparatus could lead to an overloading of the mucus transport capacity and result in obstructed airways. The excess mucus produced after exposure to irritants may be due to an enzymatic change within the mucus producing cells.[81]

Alterations in distribution of cell types and cellular secretions result in changes in rates of mucus production and in the biochemical composition of the mucus.[80] The importance, however, of these biochemical changes in terms of either protection of the lung, or in the pathogenesis of lung disease, remains to be seen.

The physicochemical properties of mucus and its patterns of coverage of the airways suggest some important properties in terms of its role in lung defence, and especially in terms of regional susceptibility to insults. Over large areas of the trachea and bronchi, mucus appears to form a continuous layer whose structure varies from smooth sheets to intricate three-dimensional networks of fibres. Transported in this heterogenous milieu are lysozyme, amylase bronchotransferrin, and immunoglobulins, particularly IgA, which aid in lung defence. Its physicochemical properties also predict that IgA will be concentrated on the surface.[82] The fibrous nature of the mucus may help to entrap particles and thus aid in their efficient removal. The difference in organisation of the mucus at different levels of the bronchial tree suggests that the efficiency of clearance of particulate matter may also vary, resulting in a variation of the effectiveness of the protective barrier against inhaled toxicants.

CONTROL OF MUCOCILIARY TRANSPORT

The rate of mucus transport depends on the viscosity, elasticity, and depth of the upper viscoelastic layer and, more importantly, on the viscosity and depth of the periciliary layer.[83] The beat rate of the cilia and the effectiveness of each cycle are also important. Each of these variables has some control mechanisms that can alter its function. Drugs that affect the autonomic nervous system have been shown to alter mucus transport.[78 79 84–86] Anaesthetics that act on the central nervous system affect mucus transport.[87 88] It is also sensitive to non-specific irritants,[89] neurohumoral mediators,[90] and immunological stimuli. It could also be altered by agents that alter epithelial permeability by changing active chloride transport.[90] Other agents may have a direct toxic effect on the cilia or the secretory apparatus. In addition to agents that may change mucociliary transport acutely the extent to which it is reversibly or irreversibly changed due to either disease or chronic exposure to air pollution is only beginning to be elucidated.

MEASUREMENTS OF MUCOCILIARY CLEARANCE

Since the mucociliary transport system is sensitive to inhaled irritants and to many other agents, determinations of normal mucociliary clearance can only be made using techniques that perturb the system as little as possible. The best data have been generated using external radiation detectors to measure the retention and transport of inhaled radionuclide labelled aerosols which are insoluble and delivered without extraneous carrier gases. Such techniques have been used by Albert *et al*,[61 91] Camner *et al*,[92] Lourenco *et al*,[93] and Foster *et al*.[79] Some investigators have delivered aerosol in which xylene or methylisobutyl ketone vapours are also inhaled.[94 95] The effect, however, on mucus transport of short-term exposures to these vapours is not known. Other authors have used an aerosol of human serum albumin.[21 96–98] Albumin has a molecular weight of 60 000 and thus will be removed from the lung both by mucociliary transport and by diffusion across epithelial barriers. The tags may also leave the particles with a half-life of $\sim$1 day. It is difficult to interpret the thoracic clearance depicted by these curves in terms of the clearance of particulate matter.

The shape of the lung retention curve depends not only on the rate of mucus transport in each airway, but also on the pattern of aerosol deposition and the geometrical counting efficiencies for particles in each region. The pattern of deposition is dependent on the size distribution of the aerosol, the pattern of inhalation, and the sizes and configuration of the airways and, therefore, retention at 24 hours varies considerably from person to person. An estimate of tracheobronchial deposition is obtained when this

24-hour retention is subtracted from the initial lung deposition.

The detector configurations affect the shape of the retention curve. The lung contains a complex three-dimensional pattern of branching airways in varying depth, and the geometrical efficiency at which each of these airways is counted will vary. The detecting system with the best spatial resolution (1-2 cm) is the gamma camera. In-vivo reproducibility of regional deposition patterns may be measured. This system, however, also requires the use of larger amounts of radioactivity (that is, >100 μCi ^{99m}Tc). Scanning scintillation systems, which have somewhat poorer spatial resolution, require ~ 30 μCi ^{99m}Tc.[99-101]

Stationary collimated scintillation detectors give little information on intrathoracic distribution but are by far the most sensitive presently in use. They require only about 0·5 μCi of ^{99m}Tc tag when used within a low background room, and can provide accurate measurements of thoracic retention through the clearance interval. Furthermore, by appropriate design of the collimation, they may be used to obtain measurements of thoracic particle retention that are essentially independent of the particle distribution within the thorax. Figure 10 shows particle retention curves for inert, insoluble γ-tagged monodisperse particles in the hours after a one-minute inhalation exposure for four different non-smoking healthy men. Clearance rates vary widely, even when the amounts cleared are comparable. On the other hand, clearance rates are quite reproducible in a given individual when the same particle size is inhaled, and vary systematically with changes in particle size and the concomitant changes in deposition pattern (fig 11).

Tracheal mucociliary transport rates may be measured by observing the passage of local concentrations of deposited aerosol; Yeates *et al*[78 102] observed mean rates of 4·7 ± 3 mm/min using 42 subjects and 5·9 ± 3 mm/min using 14 subjects. Mucus transport rates in the trachea,[78] and bronchial clearance half times in the lungs, have similar wide variability.

The wide variation of mucus transport is not likely to be due to variations in ciliary beat, since almost all measurements fall within the range of 1000-1200 beats. If the effective stroke of a cilia is 5 μm and it beats at 1000/s, then mucus will be transported at 5 mm/min, which corresponds to the average values of 4·7 and 5·9 mm/min measured by Yeates *et al.*[78 102]

It could be postulated that the similar inter- and intra-individual variations in tracheal transport

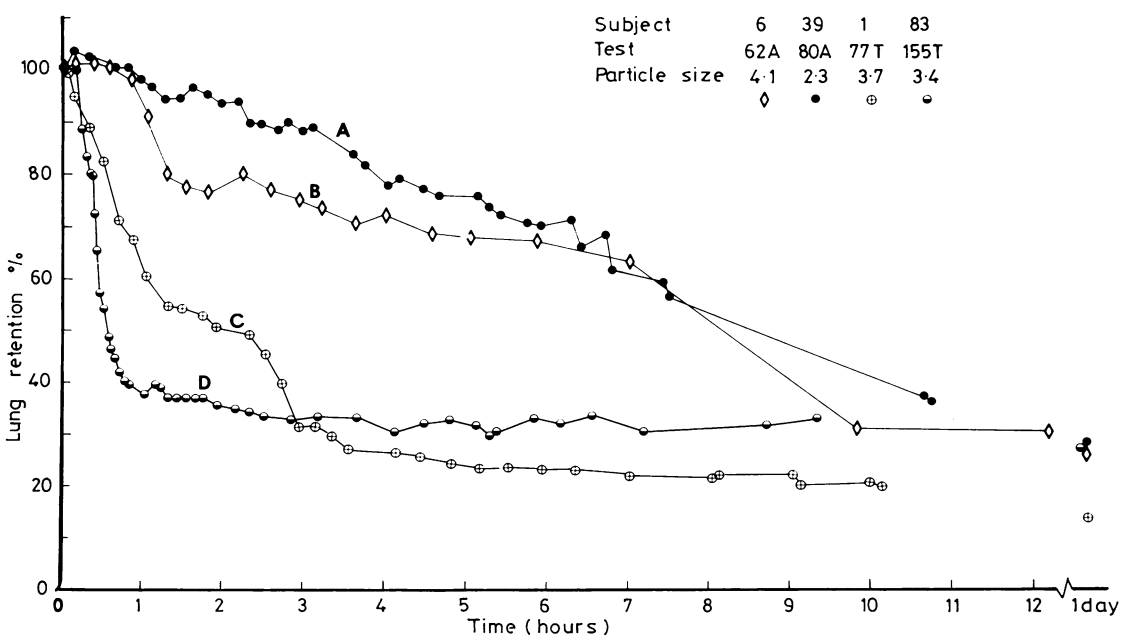

Fig 10 *Retention of γ-tagged, monodisperse ferric oxide microspheres as a function of time after a one-minute inhalation exposure via mouthpiece, for four healthy non-smoking men.*

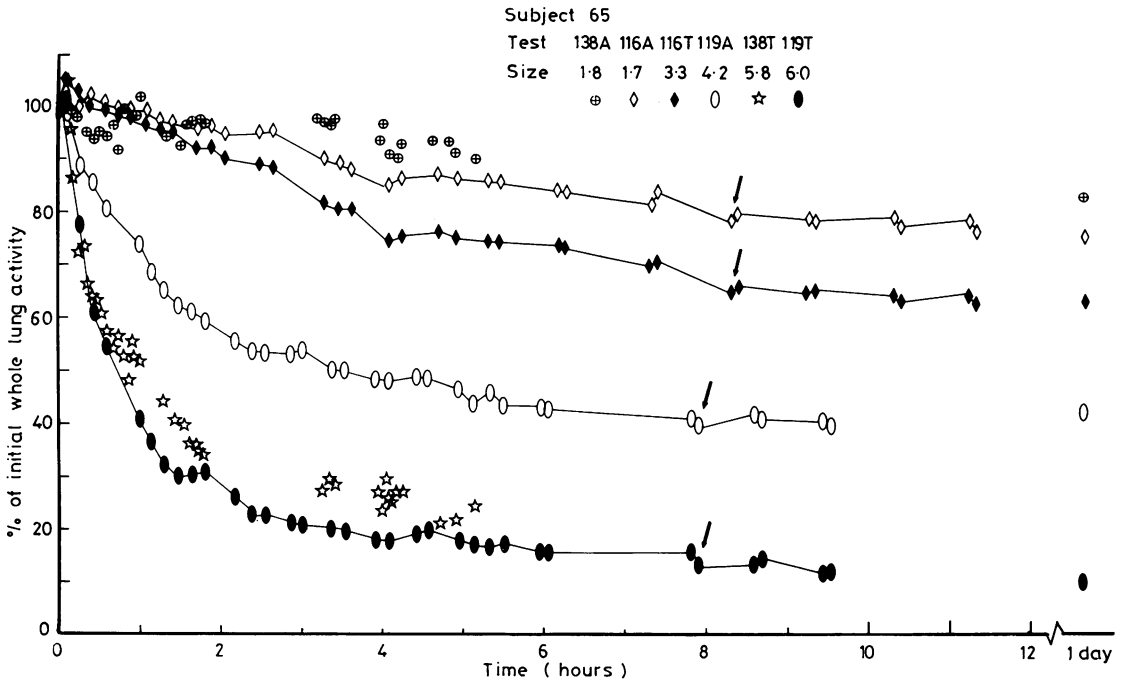

Fig 11 *Retention of γ-tagged monodisperse ferric oxide microspheres of various particle sizes for a single non-smoking man participating in a series of inhalation tests. Fraction of inhaled particles cleared by mucociliary clearance varies systematically with particle size, but effective duration of bronchial clearance phase is relatively independent of size.*

rates—that is, 25% and 75%—could be related to similar inter- and intra-individual differences in mucus viscosity, which are 30% and 60% respectively.[103] This, in turn, may be related to the variations of mucus types within cells. Ross and Corrsin,[83] however, have shown theoretically that relatively large changes in mucous viscosity result in small changes in transport rates. They suggest that mucociliary transport is more sensitive to changes in the depth and viscosity of the periciliary layer. Thus substances that optimise increases in this layer may increase mucus transport. Hypertonic saline, administered in aerosol form, could be expected to increase the depth of this layer and speed transport. Such an increase in transport rate has recently been reported by Pavia *et al.*[101]

The variability of mucus transport appears to increase proximally. Albert *et al*[61] have reported an inter-individual variation of 30% for the time at which 90% of the activity is removed from the airways (presumably as a measure of small airway clearance). Yeates *et al*[102] have recorded a variation in tracheal mucociliary transport rate of 51%.

Clearly, the rate at which seemingly healthy individuals clear deposited radioaerosols from the lungs varies widely. In people with chronic obstructive pulmonary disease there is a somewhat wider variation between individuals. The within-subject variation, however, is greatly increased,[102] which suggests that loss of control of mucociliary transport could cause or result from chronic obstructive lung disease, or both.

EFFECTS OF POLLUTANTS ON MUCOCILIARY TRANSPORT CIGARETTE SMOKE

The studies reporting effects of smoking on mucociliary transport have been confusing due to the wide variation of effects that tobacco smoke produces on the animal models studied.[104] In man the immediate response to "normal" smoking has been either an increase in tracheobronchial clearance, or no effect.[61 78 92] In the donkey low acute levels of cigarette smoke accelerated clearance,[105] but impairment of clearance was observed at higher levels.[91] The relative increase in transport is greater in the small airways,[106] which may be partly due to the adrenergic stimulation caused by tobacco smoke.

Chronic smoking appears to have a more variable effect on mucociliary transport. Yeates *et al*[78] have shown that tracheal transport rates were within

normal limits in nine smokers studied. Although rapid clearance has been observed in some long-term smokers, impairment of large airway clearance has been suggested by Albert *et al*,[91] Bohning *et al*,[107] Camner and Philipson,[108] and Lourenco *et al*.[93] Pavia *et al*[95] and Thomson and Pavia[94] were unable to show any effect on bronchial clearance of long-term smoking. Albert *et al*[6] showed that some heavy cigarette smokers had long overall bronchial clearance times, which could be interpreted as slow clearance in small airways. Faster clearance has been observed in smokers studied three months after cessation of smoking.[109] Chronic high-level exposure to cigarette smoke has been found to impair severely bronchial clearance in the donkey,[110] with recovery that was almost complete within a few weeks after cessation of smoking.

SULPHUR OXIDES

In-vivo exposures to sulphur dioxide at concentrations measured in the ambient air are not likely to affect mucociliary clearance. At higher levels, more typical of some occupational exposures, effects have been observed. Wolff *et al*[98] exposed nine non-smokers to 5 ppm (13 mg/m^3) of SO_2 for three hours after a ^{99m}Tc tagged albumin aerosol exposure. The tracheobronchial mucociliary clearance of the tagged aerosol was essentially the same as in control tests, except for a transient acceleration at one hour after the start of exposure to SO_2. Further tests by Wolff *et al*[111] showed that exercise accelerates bronchial clearance, and 5 ppm of SO_2 during exercise significantly speeds clearance beyond that produced by the exercise alone.

High concentrations of SO_2 can slow bronchial clearance. Thirty-minute exposures to SO_2 via nasal catheters produced delayed bronchial clearance and severe coughing and mucus discharge via the nose in donkeys when the concentration exceeded 300 ppm.[112] Mean residence times after exposures of 53-300 ppm were not significantly different from control test levels. The one test performed at a lower concentration (27 ppm) produced an acceleration in bronchial clearance, which would be consistent with the clearance accelerations seen by Wolff *et al*[98 111] with 5 ppm exposures. These results—that is, an acceleration at low concentrations and a slowing at higher levels of exposure—are similar to those produced by cigarette smoke.

Fairchild *et al*[113] showed that four-hour exposures to high concentrations of H_2SO_4—that is, 15 mg/m^3 of 3·2 μm CMD droplets—reduced the rate of ciliary clearance of a tagged streptococcal aerosol from the lungs and noses of mice. At concentrations of 1·5 mg/m^3 of 0·6 μm CMD droplets, there were no significant effects.

Schlesinger *et al*[114] showed that one-hour exposures to submicron sulphuric acid mist at concentrations in the range of 200-1000 μg/m^3 produced transient slowings of bronchial mucociliary particle clearance in three of four donkeys tested. In addition two of the four animals developed persistently slowed clearance after about six acid aerosol exposures. Similar acid exposures had no effects on regional particle deposition or respiratory mechanics, and corresponding exposures to ammonium sulphate had no measurable effects. In subsequent tests the two animals showing only transient responses, and two previously unexposed animals were given daily one-hour exposures, five days a week, to submicron sulphuric acid mist at 100 μg/m^3. Within the first few weeks of exposure, all four animals developed erratic clearance rates—that is, rates which, on specific test days, were either significantly slower than or significantly faster than those in their pre-exposure period. The degree and the direction of change in rate, however, differed to some extent in the different animals. The two previously unexposed animals developed persistently slowed bronchial clearance during the second three months of exposure and during four months of follow-up clearance measurements, while the two previously exposed animals adapted to the exposures in the sense that their clearance times consistently fell within the normal range after the first few weeks of exposure.

The sustained, progressive slowing of clearance observed in two initially healthy and previously unexposed animals is an important observation, since any persistent alteration of normal mucociliary clearance can have important pathological implications.

Short-term inhalation exposures of healthy human volunteers to sulphuric acid mist produced consistent results in a study by Leikauf *et al*.[115] Twelve healthy non-smokers inhaled 1/2 μm (σ_g = 1·9) H_2SO_4 at 0 (control), 100, 300, and 1000 μg/m^3 for one hour via nasal mask in random sequence on four separate days.

No consistent changes in respiratory mechanics were observed after H_2SO_4 exposure at any level, but mucociliary clearance was appreciably altered. In individuals whose control run tracheobronchial clearance half-times were greater than the mean, there was an increased rate of bronchial clearance ($p \leq 0{\cdot}02$) after exposure to 100 μg/m^3. After exposure to 1000 μg/m^3, clearance was slowed ($p \leq 0{\cdot}03$). At 300 μg/m^3 there was a wide range of response with increases in some and decreases in others.

INERT PARTICLES

The only study that examined the effect on human tracheobronchial mucociliary clearance of a heavy acute exposure to particulates is that of Camner *et al.*[116] They showed either no effect or a slight increase in mucociliary transport (presumably in large airways) in studies of eight subjects exposed to 20 breaths of 11-μm carbon particles at a concentration of 50 mg/l.

Andersen *et al*[117] studied nasal mucus flow, airway resistance, and subjective response in 16 young healthy subjects during five-hour exposures to 2, 10, and 25 mg/m^3 of a fully polymerised plastic dust containing carbon black. No significant changes in nasal mucociliary clearance rate or nasal resistance were observed. At all dust concentrations there was a decrease in one-second forced expiratory volume, but not in the forced vital capacity or the forced expiratory flow during the middle half of the forced vital capacity. The nasal penetration fraction of particles was about 55% for the smallest and 20% for the largest. Discomfort was proportional to the concentration of dust, but lagged almost two hours behind the changes in dust concentration. The main complaint was dryness in the nose and pharynx.

MUCOCILIARY TRANSPORT AND LUNG DISEASE

The tracheobronchial tree can be subdivided into subregions, each of which is susceptible to viral and bacterial infections in addition to other disease processes that could be due to or cause perturbations in mucociliary clearance. Cancer of the larynx and large bronchi could be either due to their greater relative surface density of deposition of particles,[51 52] to long residence times in these regions,[118] or to a combination of both. Small airways are presumably more susceptible to chronic obstructive lung disease that affects mucous gland hypertrophy, goblet cell hyperplasia, bronchoconstriction, oedema, and airway closure. The relation between mucociliary transport rates in the trachea, large and small airways, and the relation of these rates to disease processes remains unknown.

It is evident from numerous in-vitro and in-vivo studies that the mucociliary system can transport particles of a wide range of sizes, < 1 μm to > 500 μm in diameter, and of various types, such as charcoal, soot, lycopodium spores, cells, 680 μm diameter Teflon discs, ion exchange resins, and iron oxide, protein, polystyrene, and Teflon spheres. Whether all these types of particles are removed as effectively in each of the various ciliated regions of the human respiratory tract has not been established.

Within the airways of the lung, Hilding[118] showed that ciliastasis was often seen at the bifurcations of the larger airways. Schlesinger *et al*[114] and Bell[119] have shown that these are also sites of enhanced particle deposition. Whether bronchial cancers are initiated by irritation or cellular injury caused by deposited particulate matter on the epithelium, including radiation from radon daughter particles, has not been directly shown. Although the increased prevalence of bronchogenic carcinoma in men compared with women is currently thought to be due to differences in an environmental exposure, it is becoming apparent that there may be fewer women with slow mucociliary transport.[61 78]

The importance of defects in mucociliary transport in the pathogenesis of lung disease is unclear. Particles with biological activity, such as bacteria, can be inactivated by the immunological and enzymatic activity of the fluid lining the lung, alveolar macrophages, or other free cells in the lung. Tracheobronchial clearance studies in patients with chronic lung diseases:[6] Camner *et al*,[120] Luchsinger *et al*,[121] Matthys *et al*,[122] Sturgess *et al*,[123] Thomson and Pavia,[94] and Wagner *et al*[124] have reported faster similar and slower transport than in healthy subjects. The rapid disappearance of deposited aerosol seen in some patients was probably due to their more proximal deposition patterns or to coughing, or both, which can aid in eliminating mucus from the lungs in diseased people.[120 125] It is also possible, however, that faster transport could result from infections[126–128] that damage human ciliated epithelium in culture.[129] In these acute studies major hypertrophy of mucous glands would not be expected. This resultant defective transport may make patients with lung disease more susceptible to insults from inhaled pollutants.

Presumably the mucociliary system can cope with a considerable increase in secretions above the normal baseline level, but the relation between mucus volume transported and the surface transport rates is not known. Refluxing of mucus has been reported.[6 78 125 130] This could have been because the mucus became too thick for the cilia to propel, or to the loss of cilia as has been observed in bronchitic rats.[131] In bronchitic man, mucus in the trachea and larger bronchi may be cleared by coughing in contrast to healthy non-smoking adults in whom cough appears to have little effect.[78 125] Coughing is not believed to have much effect in small airways although this has not been shown.

The nature of the protective barrier of mucus that the airway presents to inhaled toxicants is altered in disease. This has been shown in bronchitic rats by Dalhamn[17] and Iravani.[131]

The study of mucous glands and their hypertrophy[77 132 133] has been of major importance in understanding the pathogenesis of chronic bronchitis

and chronic obstructive pulmonary disease. Reid,[132] however, measured only gland-to-wall ratios and not the physiologically important ratios of gland volume/airway circumference and gland volume/lumen size. Some work using this latter ratio has been reported by Bedrossian *et al.*[134]

The following is proposed as the possible sequence of events leading to chronic obstructive pulmonary disease. It is similar to that suggested by Albert *et al.*[61] Acute high level exposures to particles increase mucus production and mucociliary transport. Continuation of these exposures leads to bronchial mucous gland hypertrophy and goblet cell hyperplasia. Mucus transport in small airways might be expected to be normal or increased during this stage. As gland hypertrophy continues, the mucociliary transport system becomes inadequate in removing the excess secretions. This leads to chronic cough, accumulation of secretions, and further susceptibility to inhaled particulates, noxious gases, and pathogenic organisms.

Thus airborne particulates may be concerned in chronic lung disease pathogenesis: (1) as casual factors in chronic bronchitis; (2) as predisposing factors to acute bacterial and viral bronchitis, especially in children and cigarette smokers; and (3) as aggravating factors for acute bronchial asthma and the terminal stages of oxygen deficiency (hypoxia) associated with chronic bronchitis or emphysema or both.

Alveolar clearance

ALVEOLAR CLEARANCE MECHANISMS

Once a material is deposited on the respiratory epithelium of the alveoli, clearance occurs through two processes. These can be termed absorptive and non-absorptive. Both processes probably occur together or with temporal variations.

Respiratory absorption is poorly understood from a mechanistic point of view, but evidence exists for both passive and active transport.[135] Collectively, these processes bring about what appears to be a unique and selective permeability for the respiratory epithelium compared with other epithelia.[136] Permeation of the alveolar epithelium precedes both lymphatic transport and uptake into the blood. Thus both of these pathways also require the penetration of an endothelial barrier; this barrier is generally more variable and permeable than the epithelial surface.[137]

In the non-absorptive category materials may become fixed within the parenchymal tissue. Such depots may represent chemically or physically altered material, or material that has been concentrated by cytological or physiological processes or both. These depots often appear to undergo little clearance by non-absorptive processes, but, conceivably, both the normal turnover of cells and endocytosis affect their persistence.

The most widely-accepted non-absorptive clearance mechanism in the alveolar region is phagocytosis by macrophages.[138] Many investigations have been made into the role of the alveolar macrophage in dust clearance[138-141] and on its other roles—for instance, maintaining alveolar sterility and as an aetiological factor in pulmonary disease.[141 142] Efforts to evaluate the macrophage response in quantitative terms have used "free-cell harvest" by endobronchial lavage[138 143 144] and histological examinations and subsequent cell removal as the dominant non-absorptive clearance mechanism. It has, so far, not been adequately described in quantitative terms. For example, there are conflicting data on the effect of particle size on phagocytic uptake by rabbit alveolar macrophages. Holma[145] found uptake to decrease with particle size, while Hahn *et al*[146] found the opposite. Holma's smallest particles were 1·5 μm, while Hahn's largest were 2·2 μm. The results could be consistent if uptake peaked at $\sim$ 2 μm.

The clearance pathways for phagocytosed particles remain controversial. It is generally agreed that macrophages ingest particles and transport them proximally on the bronchial tree to be swallowed. There is considerable disagreement, however, on the predominant pathway between the alveoli and the bronchial tree. There are proponents for an interstitial route, while others favour a continuous proximally moving surface film that draws the cells on to the ciliated surface at the terminal bronchioles.

The interstitial route was proposed by Brundelet[63] on the basis of microscopic sections of rat lungs containing dye particles. He proposed that particle laden alveolar macrophages migrated on to ciliated airways through lymphoid collections at the bifurcations of bronchi and bronchioles. Green[147] reported similar observations for macrophages containing coal-dust, and proposed that alveolar fluid, cells, and particles flow within "liquid veins" between alveoli. The driving force for the fluid flow is the variation in the tension in the alveolar walls created by respiratory movements. This acts to move the fluid from the midzonal portion of the lobule toward areas of least pressure adjacent to subpleural, paraseptal, and peribronchial lymphatics. Tucker *et al*[64] reported that bare particles follow this clearance route in the first few hours after dye particle inhalations.

The surface route was proposed by Macklin[148] and was favoured by Hatch and Gross.[30] It has received experimental support from studies by Ferin[139] and Sorokin and Brain.[149] Ferin[139] exposed rats by

inhalation to TiO_2 and studied lung sections of animals killed at one, eight, and 25 days. These exposures were at 15 or 100 $\mu g/m^3$ levels representative more of ambient air pollution than occupational dust exposures. Particle-laden macrophages were concentrated in alveolar ducts and at junctions of respiratory and terminal bronchioles. In a follow-up study Ferin[150] used much higher concentrations of TiO_2. With increasing lung dust content, particle translocation to the lymphatic system increased faster than the total clearance rate. The clearance rate (μg/day) at day 25 postexposure increased with increasing lung deposits, but reached a plateau at a lung load of ~40 mg. Thus increasing dust burdens affect macrophage-related lung clearance.

Sorokin and Brain[149] investigated clearance pathways by a serial static histological evaluation of sections of mouse lungs after a single inhalation exposure of a polydisperse ferric oxide and cleared by the surface migration of the dust-laden cells, the duration and rate of clearance varied with the aerosol exposure duration and concentration.

The studies of Brundelet,[63] Green,[147] and Tucker *et al*[64] entailed massive exposures, and thus their conclusions about clearance pathways may not be applicable to normal conditions.

If the initial rapid phase of alveolar clearance is due to uptake by phagocytic cells and subsequent clearance of these cells via the bronchial tree or lymphatic routes or both, then it should be influenced by factors affecting the numbers of lung macrophages. LaBelle and Brieger[143] showed a strong correlation between the amount of clearance of intratracheally instilled particles and the number of phagocytic cells visible in sections of the alveolar region of the rat. They could increase the amount of clearance of uranium dioxide particles taking place within 48 hours from ~20% to ~80% of that instilled by increasing the mass of particles from 5 μg to 1500 μg with added carbon. The added carbon, however, did not affect the clearance half-time, which remained at 17 hours. Further increases in the mass loading caused congestion and reduced clearance. The addition of carbon particles apparently stimulated the release of macrophages. LaBelle and Brieger[144] showed that the number of phagocytic cells recovered in lung washings was proportional to the amount of carbon that was either instilled or inhaled, although the amounts inhaled were not specified.

Brain[138] confirmed that increased deposition of inhaled particles is followed by an increase in the number of recoverable free cells. For acute exposures, he found an increase in cell count within hours, which reached a maximum at about one day, and then gradually disappeared. For six rats exposed for seven hours to a monodisperse triphenyl phosphate aerosol with a median diameter of 0·55 μm and a mass concentration of 21 mg/m^3, the exposure increased the number of recoverable cells after 12 lung washings by 122% as compared with a group of six control rats ($p = 0{\cdot}001$).

Brain and Corkery[151] developed a technique for determining the in-vivo rate of colloidal ^{198}Au particle ingestion by pulmonary macrophages in hamsters. The particle and cell contents are determined in 12 successive lung lavages. The first six washings are made with a balanced salt solution containing divalent cations that removes most of the free particles but few cells. The next six washings are made with physiological saline that recovers most of the available pulmonary macrophages. The degree of particle ingestion is determined by comparing the particle content in the first six washings with that of the second six, where the recovered particles are within the macrophages. They found that essentially all of the gold colloid is ingested within about six hours. Pre-exposure to ferric oxide, colloidal carbon, or coal dust reduced gold colloid uptake by macrophages as measured two hours later. When gold colloid uptake was measured 24 hours later, it was within normal limits after exposure to ferric oxide and colloidal carbon. The coal dust exposure, however, caused as great a depression in gold uptake at 24 hours as it had at two hours. Thus while various dusts can competitively inhibit endocytosis, only toxic dusts, such as coal, exhibit a toxic and persistent effect on macrophage function.

Bingham *et al*[152] exposed rats by inhalation for up to four months to a relatively low (2 mg/m^3) concentration of respirable coal dust from either Utah or Pennsylvania. Neither dust produced a significant increase in the number of alveolar cells obtainable by lung lavage, but both decreased the bactericidal properties of the lavaged cells.

The quantitative relations between the number of free cells recoverable by lung washing and the amounts and rates of clearance of particles deposited in the alveoli have not yet been established for either inert or cytotoxic dusts. Strecker[153] exposed rats to TiO_2, Al_2O_3, and Fe_2O_3 dusts by inhalation. The average deposition was about 500 μg per lung and the increase in the number of alveolar macrophages showed only a slight transient increase, which corresponded roughly to the number of cells containing dust. Quartz dust in similar exposures produced a pronounced increase in cells and cell division. Strecker[153] interpreted the increase in the number of cells containing the non-fibrogenic dusts as indicating a slowdown of transport of dust loaded cells to the ciliated bronchial tree—that is, cells containing dust are less rapidly cleared than the dust-free cells

concerned in the normal turnover.

There are other forms of endocytosis, such as pinocytosis, which cannot be easily differentiated from true absorption inasmuch as they both may account for the transmembrane transport of a material. Thus any description of an absorptive process that cannot be precisely localised and made on a mechanistic basis, clearly the predominant situation, must be considered tentative and uncertain both as to the number and types of transport mechanisms operating. Absorptive clearance of inhaled materials from the alveolar surface is consequently largely based on, or inferred from, the ultimate disposition of the material, especially its appearance in the blood, other body organs, and the urine.

Bona fide absorptive mechanisms and pathways have been established for specific materials in the alveolar membrane, and it is tempting to generalise these. Specific information on alveolar absorption mechanisms comes mainly from the studies of Chinard,[136] Taylor *et al*,[154] Liebow,[155] and Bensch and Dominguez.[156] Other relevant data, generally lacking mechanistic information, are available on specific materials.[157]

TRANSLOCATION OF PARTICLES WITHIN THE LUNGS

A chronic phase of clearance, characterised by the appearance of particles within macrophages of the connective tissue compartment of the lungs begins from one to three weeks after exposure, according to Sorokin and Brain.[149] The extent of such sequestration of particles increases slowly in the subsequent weeks and months. For several months a far greater percentage of alveolar as compared with connective tissue macrophages store ferric oxide particles, but ultimately whatever remains uncleared from the lungs resides in the connective tissue. The fate of cytotoxic particles may differ from that of relatively inert particles, such as ferric oxide.

Davis *et al*[158] compared lung dust with airborne exposure levels and pathological findings in 74 coal miners. Men who developed pulmonary massive fibrosis (PMF) and those who developed the more severe forms of simple pneumoconiosis retained similar amounts of total dust, but the PMF lungs retained more quartz.

The internal redistribution of particles retained within the lung is an important factor in determining the site of damage. Redistribution is apparent in the case of centrilobular accumulation of pigment, which is seen on the cut surfaces of human sections.[159–161] Such a focal accumulation of particles can also influence their retention and pathogenic potential, at least in the case of fibres longer than about 10 μm.

For low mass concentrations of short fibres that were neutron activated, Morgan *et al*[162] found that there were no significant differences between amphibole and chrysotile asbestos in in-vivo retention in the rat. Autoradiographs of lung sections indicated that the initial deposition was uniform right out to the lung periphery, while over a few months the fibres accumulated in foci that were mainly subpleural.

In subsequent experiments Morgan *et al*[163] administered radioactive asbestos to rats by inhalation. After exposure, the animals were killed serially, and the lungs were subjected to bronchopulmonary lavage. Initial washes were made with a balanced salt solution that removed free fibre and cells from the conducting airways. Subsequent washes were made with physiological saline that recovered cells originally present in the alveolar spaces. The number of cells and the amount of fibre recovered in each wash were measured. About 20 μg of fibre was deposited in the lung and appeared to have no significant effect either on the number of free cells in the lung or on their size. Uptake of fibre by alveolar macrophages was effectively complete after 24 hours. Analysis of the results suggests that fibres that are much longer than the diameter of the alveolar macrophage (~ 12 μm) find their way into the alveolar wall from where they cannot be recovered by lavage. This process is complete within two weeks of exposure.

Wright and Kuschner[164] used short and long asbestos and man-made mineral fibres in intratracheal instillation studies in guinea pigs. With long fibres, all of the materials produced lung fibrosis, although the yields varied with the materials used. With equal masses of short fibres, however, of equivalent fibre diameters, none of the materials produced any fibrosis.

The reason that short fibres are less damaging appears to be because they can be fully ingested by macrophages.[165] Longer fibres can rupture the macrophage membrane with release of digestive enzymes or loss in mobility or both.[166]

Most inhalation studies have been performed with aerosols containing both short and long fibres, and it should be noted that the responses may be related primarily to the initial burden or persistence, or both, of the longer fibres. For example, Middleton *et al*[167] exposed rats to UICC standard reference samples of amosite, crocidolite, and chrysotile A at concentrations of 1, 5, and 10 mg/m^3, and killed them serially over the next four months. They found less retention of chrysotile than of the amphiboles, and that the clearance of the amphiboles appeared to be dose related.

The mechanism for the observed peribronchiolar

accumulations in the lung is not clear. Gross *et al*[168] exposed rats to high (> 1000 mg/m^3) concentrations of quartz dust and some non-fibrogenic dusts. Four days later the peripheral alveoli were cleared, but the alveoli leading from respiratory bronchioles and alveolar ducts were occluded by dust. The localisation was attributed to the respiratory bronchiole being analogous to the neck of a funnel on the basis that the surface area of the air spaces more distal are roughly 500 times greater. This circumstance was said to explain the vulnerability of the bronchiole to inhaled pollutants and the initial localisation of lung disease at such sites.

Heppleston[169] exposed rats and rabbits daily for several weeks to coal and haematite dusts in a serial death study. For both materials, he found that most of the dust is rapidly taken up by phagocytes. It was initially scattered in peripheral alveoli, but gradually formed more discrete focal collections in more proximal alveoli that open into and surround respiratory air passages. The dust foci were particularly well defined in the rabbit. Some animals received two separate exposures; one to coal and one to haematite. The results did not depend on which was inhaled first. Early in the second exposure, small amounts of the second dust were incorporated into the periphery of foci of the first dust, and as survival after both exposures lengthened, a progressive mixing of the two dusts extended towards the centres of the foci. A minor and diminishing fraction of the total dust in the lung was scattered in peripheral alveoli, mostly in phagocytes, but some in free cells. Dust within cells and outside was occasionally seen in the mucosa of the air passages. The hilar lymph glands contained large and small aggregations of dust. The quantity of the first dust exceeded the second and was more centrally concentrated in the aggregations. Heppleston concluded that, so far as he could judge from microscopy, the double exposures had a simple additive effect, and there was no evidence that elimination of one dust is prompted by subsequent exposure to another.

Among the many aerosol factors that can influence alveolar particle clearance are exposure concentration, exposure duration, and aerosol composition. Civil *et al*[170] conducted an extensive series of inhalation studies on rats with coal dusts of various ranks. They found that intermittent exposures do not appear to constitute a significantly greater hazard than equivalent continuous exposures. Coal rank had some influence in that the pulmonary retention was consistently greater with high rank coal dust. There were differences in the patterns of clearance among high ranked dusts, but not with low ranked dusts.

Pneumoconiotic lesions do not appear to retard alveolar particle clearance. Heppleston[161] reported that deposition of inhaled magnetite particles in rats with pneumoconiotic lesions from prior coal or silica inhalations took place more rapidly than in normal rats, with much of the dust passing through focal accumulations of the pre-existing aggregates of coal or silica.

The hold-up of dust in the peribronchiolar region observed by Heppleston *et al* appears to be consistent with the previously cited hypothesis of Strecker[153] concerning the reduced rate of clearance of phagocytes containing dust.

Accumulation of particles in the peribronchiolar region can occur normally in man without gross or acute exposures. Lung sections of 653 veterans necropsied at the Durham, NC, Veterans Administration Hospital between 1967 and 1969 were examined by Pratt and Kilburn[159] for the degree of accumulated pigment. The population included smokers and non-smokers, and urban and rural dwellers. All showed some pigment accumulations, although the extent of pigmentation was significantly greater in smokers compared with non-smokers and in city smokers compared with country smokers. In all cases the pigment, presumably due to insoluble particles, was concentrated in small foci and not uniformly distributed over the lung. The locations of the concentrated pigment appear to be consistent with the characteristic locations of peribronchiolar emphysema.

TRANSLOCATION OF PARTICLES TO LYMPH NODES

Particles that penetrate the alveolar surface can migrate through the lymphatic drainage system to pleural, hilar, and tracheal lymph nodes. The migration is, however, very slow. Ferin[139] found negligible accumulation of TiO_2 in the lymphatics at 25 days. Sorokin and Brain[149] reported that significant build-up of ferric oxide particles in the lymphatics did not take place until nearly a year after the aerosol exposure. On the other hand, Thomas[171] reported that with radioactive particles the concentration of particles in the lymph nodes exceeds the lung concentration several months after the end of the inhalation. Ferin[150] found that the fraction of lung dust cleared via the lymphatics increased with total lung burden of dust.

TRANSLOCATION BEYOND THE THORAX

Materials deposited by inhalation can usually be found in measurable quantities in other organs. In most cases the presumed pathway is the bloodstream following gradual solution in lung fluids and diffusion into pulmonary capillaries. Absorption presumably depends on materials being mainly in

a monomeric state or, to a lesser extent, in polymeric forms of small dimensions.[134] Some in-vitro solubility models[157 172] have proved useful in predicting in-vivo clearance rates, but at other times they provide inconsistent or erroneous estimates. Further work is needed to improve these models and thereby their usefulness.

ALVEOLAR CLEARANCE KINETICS

The clearance of particles deposited in the alveolar region proceeds in several temporal phases, which can usually be described by a series of exponentials, with each presumably corresponding to a different clearance mechanism.

Casarett[173] proposed that the earliest alveolar phase, with a half time measured in weeks, is generally associated with phagocytic clearance, while a slower phase, with a half time in months or years, is generally associated with solubility. The Task Group model[33] does not include the initial alveolar phase, which Casarett attributes to their over-reliance on data from studies in which the fast alveolar phase was absent because of the cytotoxicity of the dusts used. Jammet[174] showed that for haematite dust, a clearance phase with a half time of from 10 to 12 days is normally present in the cat, rat, and hamster preceding a slower phase with a half life exceeding 100 days. The 10-12 day phase disappeared when the animals were exposed to sufficient plutonium,[175] silica dust, or carbon dust,[176] while the half time for the slower phase was relatively unaffected.

Numerous inhalation studies have been performed on beagles with insoluble radioactive aerosols, with long-term follow-up of the lung retention by external in-vivo gamma counting.[177–180] In most, but not all of these studies, a fast phase with a half time of 10-14 days is evident. The half life for the slower phase of alveolar clearance, which appears to be related to in-vivo solubility, varies. Morrow *et al*[180] used test aerosols of $^{59}Fe_2O_3$, ^{203}HgO, $^{131}BaSO_4$, $^{54}MnO_2$, and UO_2. The biological half times for the slow alveolar clearance phases were 58, 33, 8, 34, and ~200 days, respectively. Bair and Dilley[177] found that the slow phase of alveolar clearance of $^{59}Fe_2O_3$ was greater than several hundred days, suggesting that the surface-volume ratios or other surface properties of the particles can have a major effect on solution in the lung.

Considering the recognised importance of the alveolar retention of relatively insoluble particles in the pathogenesis of chronic lung disease, it is somewhat surprising that an examination of published reports yields virtually no useful data on the rates or routes of alveolar particle clearance in man. The paucity of the data is attributable to the experimental sophistication required for, and the relatively high cost of, human studies. The only feasible way to perform such studies is to have the subjects inhale tagged test aerosols, whose subsequent lung retention can be monitored with external detectors. Human studies are further limited in the types and varieties of particles since only demonstrably non-toxic particles can be intentionally inhaled. The only experimental studies on human alveolar clearance are those of Albert and Arnett[181] and Morrow *et al*.[71 182]

In the Albert and Arnett study eight normal men inhaled neutron activated metallic iron particles. For three subjects there was sufficient residual activity after completing the bronchial clearance for continued measurement of retention. For a 32-year-old non-smoking man, and a 27-year-old man who was a moderate smoker, the post-bronchial clearance occurred in two phases, a fast phase lasting about one month, and a much slower terminal phase. The faster phase was missing for a subject who was a 38-year-old two-pack-a-day cigarette smoking man with chronic cough. While it is not possible to draw firm conclusions from these limited data, they are consistent with the recent findings of Cohen *et al*,[183] who studied the alveolar clearance rates of magnetite particles in nine non-smokers and three smokers, using an external magnetometer for the particle retention measurement. The clearance rates in all three smokers were much lower than in any of the nine non-smokers. Thus it appears that the fast alveolar phase can be detected in man, and that dust retention may be increased by cigarette smoking, beyond the retention of the smoke particulates themselves. Low doses of cigarette smoke have been shown to inhibit macrophage phagocytosis.[184]

The only other experimental human inhalation studies of alveolar clearance under controlled conditions are those of Morrow *et al*. In an initial study,[71] four normal individuals inhaled a $^{54}MnO_2$ aerosol with a median size of 0·9 μm, a geometric standard deviation of 1·75, and a mass concentration of 4 mg/m^3. The aerosol was inhaled for 20-30 minutes at a breathing pattern in which four normal inhalations alternated with a maximal inhalation. For measurements made more than 48 hours after the inhalation, a single clearance phase was found for all four individuals, with biological half times that varied only from 62 to 68 days.

In the additional human studies of Morrow *et al*,[182] using several different aerosols, alveolar clearance rates were also reported in terms of a single exponential. The half times varied with the composition of the particles used. Half times of 65, 62, and 35 days were found for $^{54}MnO_2$, Fe_2O_3 labelled with ^{51}Cr, and ^{51}Cr labelled polystyrene,

respectively. The shorter half time for the polystyrene particles may have been because it was based on less than 14 days of measurements, and, therefore, may have been more influenced by a rapid initial rate of alveolar clearance than were the iron and manganese oxides, which were followed for periods of between 45 and 120 days.

Some scattered data on human lung retention of inhaled particles is available from reports of in-vivo measurements made on atomic energy industry workers who were accidentally exposed to airborne nuclides.[179 185 186] While these data are interesting and useful for some evaluations, they must be interpreted with their limitations in mind. Among these limitations are: (1) the time the exposure took place is either not known, or it extended over an indeterminate period of time before it was discovered; (2) the chemical form and particle size distribution of the inhaled aerosol are usually not known, and the exposure may be to more than one aerosol or nuclide or both; and (3) the exposure may be detected from routine bioassay or in-vivo counting at a time well after the exposure took place, thus making it impossible to establish the initial amount deposited.

This review draws in large measure on previous reviews of deposition, retention, and clearance that were prepared for the National Research Council National Academy of Sciences in Washington DC. One was in *Airborne Particles*, one of a series of monographs on the medical and biological effects of environmental pollutants published in 1979. The other review appeared in *Measurement and Control of Respirable Dust in Mines*.[187] We are grateful to the National Research Council for permission to use these materials in this form. This review emphasises the occupational health aspects of inhaled particles.

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