JOURNAL OF AEROSOL MEDICINE
Volume 1, Number 4, 1988
Mary Ann Liebert, Inc., Publishers

Lung Clearance of Inhaled Insoluble and Soluble Particles

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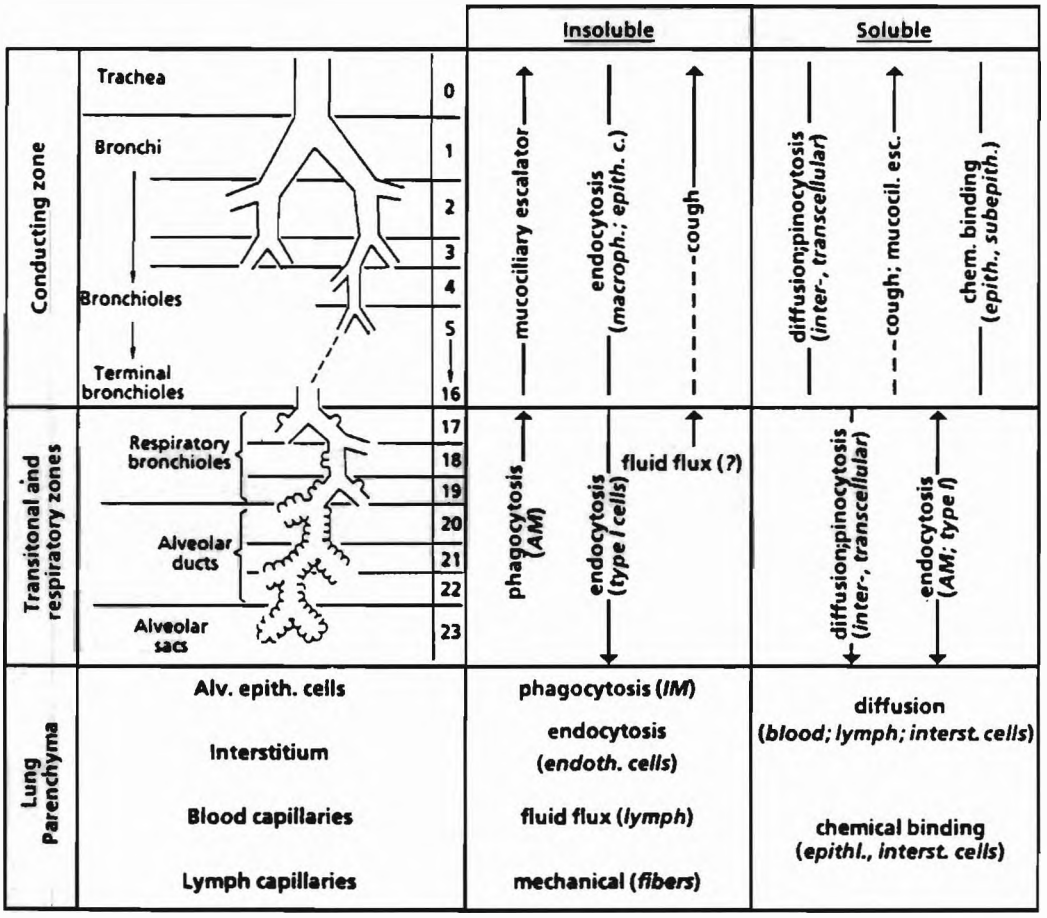
INTRODUCTION

Efficient elimination of inhaled soluble and insoluble particulate compounds deposited in the respiratory tract is necessary to keep its mucosal surfaces clean and functionally intact. In addition, the characteristic clearance processes and kinetics prevailing in different regions of the respiratory tract determine the retained dose of an inhaled substance in structures of the respiratory system. Thus, whether deposition and subsequent retention of inhaled particles is considered in clinical situations involving diagnostic or therapeutic aerosols or in toxicology with occupational or environmental pollutant aerosols, knowledge of the clearance of these substances is crucial in understanding their respiratory tract dosimetry. Clearance mechanisms are not only different for different regions of the respiratory tract, but also depend on physico-chemical characteristics of the deposited particulate material. Several recent review articles provide detailed descriptions and discussions of different processes governing the removal of inhaled solid and solute particles after deposition in the respiratory tract (Lauweryns and Baert, 1977; Morrow, 1977; Camner, 1980; Jones et al., 1982; Effros and Mason, 1983; Jones, 1984; Pavia, 1984; Morrow and Yu, 1985; Schlesinger, 1985; Brain, 1985, 1986; Cuddihy and Yeh, 1988). Because of the multitude and complexity of the diverse respiratory tract clearance processes, the present article will selectively review aspects of soluble and insoluble particle removal from tracheobronchial and deep lung regions. In addition, the article emphasizes clinical and toxicological implications of these removal processes and considers some unresolved issues related to lung clearance.

Key words: particles; tracheobronchial clearance; pulmonary clearance; solubility; alveolar macrophage; phagocytosis; particle overload; epithelial permeability

Figure 1 is a schematic overview of clearance mechanisms, separated by those for insoluble and for soluble particles. This scheme is simplified insofar as it assumes that insoluble particles are not dissolved in the lung (no in vivo solubility) and that inhaled soluble particles will not remain in particulate form after deposition in the lung (high in vivo solubility). One might predict that compounds of low water solubility are cleared from the lung more slowly than compounds of high water solubility. However, many "insoluble" particles show in vivo dissolution in the lung, very likely within the phagolysosomes of alveolar macrophages due to the low pH (Lundborg et al., 1984). Thus, many solid particles are cleared from the lungs involving mechanisms for both insoluble particles and solutes. Water solubility of an

Fig. 1: Elimination of Inhaled Particles: Clearance Mechanisms



Schematic representation of clearance mechanisms of inhaled particles deposited in the lung. "Insoluble" and "soluble" refers to in vivo solubility rather than solubility in water. Since most "insoluble" particles undergo dissolution in the lung to some degree, the dissolved material from "insoluble" particles and from solid particles with rapid in vivo dissolution will be cleared by pathways listed under soluble particles. Dissolution of particles of low in vivo solubility can become an important clearance mechanism after retention of months and years in the alveolar and interstitial compartment. The trachea and lymph/blood circulation are the final pathways for elimination out of the lung. Numbers 0-23 refer to respective generations in Weibel's lung model.

inhaled compound alone is not a good predictor of its clearance behavior in the lung. A few examples on the pulmonary retention kinetics of heavy metal compounds may illustrate this: Water soluble $NiCl_2$ is cleared from the lungs of rats rapidly (English et al, 1981) corresponding to a retention halftime of less than one day, whereas water soluble $CdCl_2$ is retained in the rat lung with a retention halftime of about two months due to chemical binding (Oberdörster et al., 1979a). As one might expect, CdO and NiO particles of very low water solubility are retained in the rat lung with a long retention halftime, which is also about two months (Oberdörster et al., 1979a; English et al., 1981). However, whereas NiO lung retention reflects probably mainly mechanical lung clearance of the NiO particles, the CdO particles are rapidly dissolved in the lung (Hadley et al., 1980) and are then cleared by the same mechanisms and at the same slow rate as $CdCl_2$. In contrast, ZnO particles of low water solubility, which are also rapidly dissolved in the lung, are cleared at a fast rate corresponding to a pulmonary retention halftime of six hours in rats (Oberdörster et al., 1979b). Thus, in vivo dissolution of a particle in the lung can be distinctly different from water solubility, but neither water nor in vivo solubility are unequivocal predictors of the pulmonary clearance rate of a compound.

Mercer (1967) proposed a clearance model based on dissolution of particles as a function of their surface area. In his model, knowledge about the particle mass distribution and the nonequilibrium solubility coefficient of the material in lung fluid is required to predict its clearance from the lung. As pointed out by Morrow (1974), such predictions turned out to be quite accurate for some particulate compounds, e.g., UO_2, yet much more information is needed before this solubility concept can be applied generally to inhaled particles. In particular, dissolution of particles in the lung is conceivably quite different depending on whether the particles are in the liquid surface layer of the epithelium, phagocytized in alveolar macrophages, in epithelial cells, or in the interstitium. For example, Lundborg et al. (1984) found increased dissolution of particles of metal oxides in alveolar macrophages, possibly due to the low pH in their phagolysosomes.

The Task Group on Lung Dynamics of the International Commission of Radiological Protection (ICRP, 1966) proposed a lung clearance model which incorporates three classes of compounds with different solubilities in the deep lung and respective retention halftimes of days, weeks, and years for D, W, and Y compounds. Both absorptive and mechanical clearance mechanisms were considered, and resulting pulmonary retention halftimes for very soluble compounds (Class D) were given as 0.5 days, for intermediate soluble compounds (Class W) as 50 days and for highly insoluble compounds (Class Y) as 500 days. With this simplified clearance model, compounds could be classified with respect to their pulmonary clearance, based solely on their physico-chemical nature.

The ICRP clearance model assumes that each clearance pathway (absorptive or mechanical) clears a particular compound at a constant rate. Thus, an ICRP general retention equation for the tracheobronchial or pulmonary compartment following a single inhalation exposure can be written as:

$$A_t = A_o \sum_n f_n \exp(-b_n t) \qquad (1)$$

(Morrow, 1977) where A_t and A_o is the amount retained at time t and time 0, f_n is the fraction of A_o cleared with each of n clearance pathways, and b_n the clearance rate for each of n clearance pathways; b_n is inversely correlated with the retention halftime $T_{1/2}$:

$$b_n = \frac{\ln 2}{T_{1/2}} . \qquad (2)$$

OVERVIEW OF CLEARANCE MECHANISMS

The main clearance pathway for insoluble particles in the tracheobronchial region is the mucociliary escalator consisting of the ciliated epithelium

moving a mucous layer on top of it. This layer is composed of a sol phase of low viscosity (hypophase) in which the cilia beat, and a blanket of an overlaying gel phase of high viscosity (epiphase) which is thought to be moved by ciliary motion towards the pharynx. Although it is generally believed that this mucous blanket is continuous throughout the respiratory tract, contrasting observations in rats have been made which led to the suggestion that this layer may be discontinuous under normal conditions and becomes more widespread only under conditions of bronchitis (Iravani and van As, 1972; van As and Webster, 1974; van As, 1980). In support of his observation of mucus islets in the conducting airways, van As (1980) reasoned that extremely high velocities of tracheal mucus would be necessary to accommodate clearance of a continuous mucous blanket originating in the terminal bronchioles with their large aggregated circumference. Obviously, such discontinuous mucous layer would make mucociliary clearance of particles deposited in the tracheobronchial region less efficient. Other investigators could not confirm the discontinuous mucous blanket, but did find a lack of the high viscosity epiphase in the bronchioles (Gil and Weibel, 1971; Luchtel, 1982) which would also reduce the efficiency of mucociliary movement in these generations. Clearance of particles depositing in the tracheobronchial region also occurs through phagocytosis by airway macrophages which are either alveolar macrophages moving up with the mucociliary escalator (Lehnert and Sanz-Rodriguez, 1988) or macrophages entering the airways via bronchial and bronchiolar mucosa (Morrow, 1974; Robertson, 1980). The importance of these macrophages for particulate clearance from the conducting airways as well as their origin needs further investigation (Brain, 1988; Gehr et al., 1988). Another clearance mechanism, which is less important in terms of the amount being cleared in the tracheobronchial region, is penetration of insoluble particles of submicronic size through the epithelium (Gore and Patrick, 1982), very likely due to endocytosis by epithelial cells of the conducting airways (Sorokin and Brain, 1974). In contrast to the results with small submicronic particles, no evidence was found that bigger particles (7.9 μm) penetrated the bronchial epithelium (Velasquez and Morrow, 1984). Finally, cough can be a very efficient clearance mechanism in the conducting airways (Leith, 1977; Köhler et al., 1986), but is probably limited to the upper generations of the conducting airways (Mossberg, 1980). However, formation of a flow limiting segment (FLS) in the trachea or upper generation bronchi due to repeated frequent coughing maneuvers could actually lead to a decrease in mucociliary clearance (Smaldone et al., 1979; Smaldone, 1986). This observation corroborates clinical experience in patients with chronic obstructive pulmonary disease and asthma who show regional defects in clearance associated with the location of FLS (Smaldone, 1986).

Soluble particles depositing in the tracheobronchial tree are mainly cleared by absorptive mechanisms consisting of transepithelial permeation via intercellular pathways (tight intercellular junctions) or by active and passive transcellular transport (Bhalla and Crocker, 1986). In addition, mechanical clearance along the mucociliary escalator or cough can contribute to tracheobronchial clearance of inhaled solutes. Chemical reactions can also influence the rates of clearance of soluble substances from the tracheobronchial tree, i.e., reactions with and binding to cellular and extracellular components.

The most effective clearance mechanism for insoluble particles in the alveolar region is phagocytosis by alveolar macrophages (AM) (Ferin et al., 1965; Green, 1973; Morrow, 1973; Hocking and Golde, 1979; Robertson, 1980; Herscowitz, 1985; van Furth, 1985; Brain, 1986) and transport in turn to the mucociliary escalator for removal towards the larynx. Some AM may penetrate back into the interstitium (Holt, 1980; Corry et al., 1984), from where the particle laden AM may reach the regional lymphnodes (Harmsen et al., 1985) although this is disputed (Adamson and Bowden, 1978; Lehnert et al., 1986). AM - particle encounters in the deep lung could be facilitated through the activation of serum components by deposited particles which then act as chemoattractants for AM (Warheit, et al., 1985, 1988). Likewise, chemotropism may be responsible for migration of AM towards the mucociliary escalator,

although such chemotactic movement has not been demonstrated (Lauweryns and Baert, 1977). Endocytosis by type I - and to a lesser degree by type II - epithelial cells and subsequent exocytosis into the interstitium is another clearance pathway in the deep lung by which deposited smaller particles and fibers can reach interstitial sites (Greenberg et al., 1972; Lauweryns and Baert, 1974; Sorokin and Brain, 1974; Brody, 1979; 1981), whereas larger nonfibrous particles (≥9 μm) are probably less likely to be translocated across the epithelium (Snipes and Clem, 1981; Snipes et al., 1984). For the removal of free particles from respiratory bronchioles and alveolar ducts a mechanical mechanism caused by a drag or fluid flux supported by continuous surfactant production, cranial movement of the mucociliary layer and the tidal respiratory movement of the lung was suggested (Macklin, 1955; Casarett, 1960; Brain, 1970; Robertson, 1980) but never proven experimentally. The result of a study by Faridy (1976) showing cranial movement of surfactant into bronchioli and bronchi during ventilation of rat lungs support this suggestion.

Transepithelial transport is the major mechanism for clearance of soluble substances from the alveolar region. Intercellular diffusional transport in the region of tight junctions as well as active and passive transcellular transport is involved (Lauweryns and Baert, 1977). Major determinants for the rate at which these absorptive processes occur are the lipophilicity and hydrophilicity of the solutes and their molecular size (Enna and Schanker, 1972a,b). Saturable, carrier type transport processes have also been described for some anionic compounds including the amino acid glycoleucine (Lin and Schanker, 1981), and for inorganic cations such as Cd a calcium channel dependent uptake into cells can exist (Hinkle et al., 1987). Other factors affecting pulmonary clearance rates of hydrophilic substances include lung volume, epithelial surface area and distribution of the substance in the epithelial surfactant layer (Effros and Mason, 1983) which will be discussed later. Endocytosis by AM and Type I epithelial cells can also contribute to solute clearance from the alveolar space of the lung, in particular for large molecular weight hydrophilic compounds (Bhalla and Crocker, 1987).

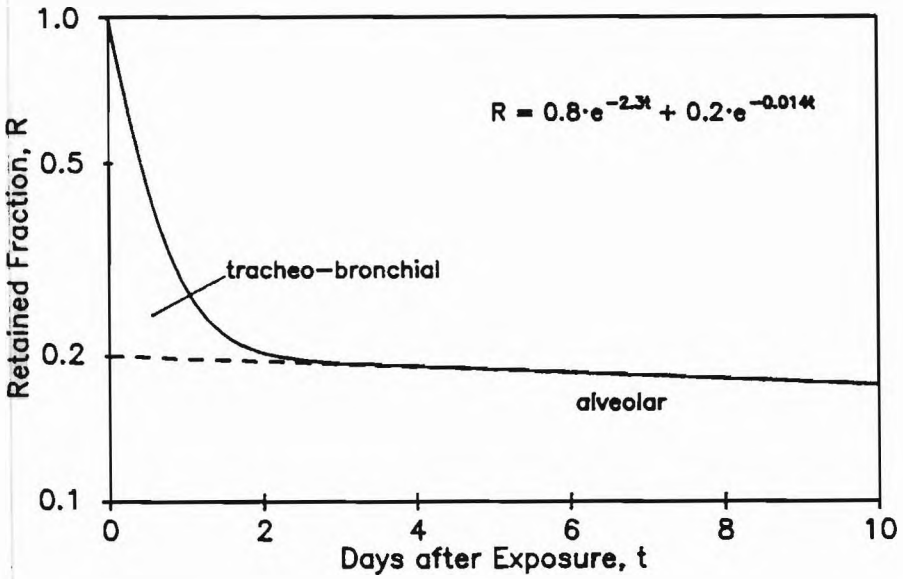
Clearance mechanisms in the alveolar space provide an effective means to cleanse the alveolar epithelium of insoluble particles. Only a small fraction reaches the interstitium under normal conditions. Once they have reached the interstitium, several mechanisms can contribute to their further removal (Fig. 1). These include phagocytosis by interstitial macrophages (IM), endocytosis and luminal exocytosis of small (< 0.1 μm) particles by endothelial cells, directed fluid flux via clefts of intercellular junctions of lymph capillaries, and direct mechanical movement (for example of mineral fibers) through the interstitium (Morrow, 1972, Lauweryns and Baert, 1977; Sebastien et al., 1979; Leak, 1980).

Water-soluble substances that reach the interstitium, on the other hand, will be cleared by diffusion into blood capillaries and to a lesser degree into lymph capillaries depending on their molecular size. The major determinants of clearance of hydrophilic solutes into capillaries are the Starling forces which result from the balance between intravascular and interstitial hydrostatic and oncotic pressures (Starling, 1896). Since the intercellular junctions of the lymph capillaries are less tight than those of the blood capillaries (Lauweryns and Baert, 1969) one would predict that larger sized hydrophilic solutes in the interstitial space - like proteins - are cleared preferentially into lymphatics. Indeed, Meyer et al. (1969) calculated lymphatic uptake to be almost 40 times more effective than absorption via blood capillaries; however, quantitatively more of such solutes were found to be cleared via the blood circulation than via lymph due to the high blood flow to lymph flow ratio (Meyer et al., 1977). Depending on the chemical nature of solutes, binding to epithelial or interstitial cell structures can occur and delay their clearance.

TRACHEOBRONCHIAL CLEARANCE

Figure 2 shows a hypothetical retention curve of inhaled insoluble particles deposited in the lower respiratory tract, i.e., from trachea to alveoli. Two

FIGURE 2
Hypothetical Retention of Particles in the Lower Respiratory Tract



It is assumed in this case that 80% of the deposited particle mass clears rapidly from the tracheobronchial tree (retention halftime 0.3 days) and 20% more slowly from the alveolar region (retention halftime 50 days). Alveolar deposition is assumed to be represented by the intercept of the slow clearance phase with the R-axis. Both tracheobronchial and alveolar retention could probably be described more accurately by increasing the numbers of exponential terms in the retention equation.

distinct phases can be distinguished, a rapid phase which in this case clears 80% of the deposited material with a retention halftime of 0.3 days and a slow phase with a retention halftime of 50 days for 20% of the deposit. The relative amount being cleared in either phase depends on the amount deposited in the tracheobronchial and in the pulmonary region, which in turn is a function of the characteristics of the particle and of breathing (Heyder, 1982). The rapid phase of clearance is usually regarded as reflecting tracheobronchial clearance, which is presumed to be essentially complete 24 hours after the exposure. As pointed out by Morrow and Yu (1985), a better fit could be achieved by a three exponential term, and additional exponents in the general equation (1) would improve the fit still more. Therefore, the numbers of exponents one could use is arbitrary since there appears to be no physico-chemical or physiologic basis for selecting a certain number. In this context, Morrow and Yu (1985) discussed also a time dependent tracheobronchial retention for which a power function could be applied to describe the retention kinetics. The use of exponential terms, however, is very convenient and appealing since they allow clearance kinetics to be expressed in terms of clearance rates and retention halftimes which are easily understandable.

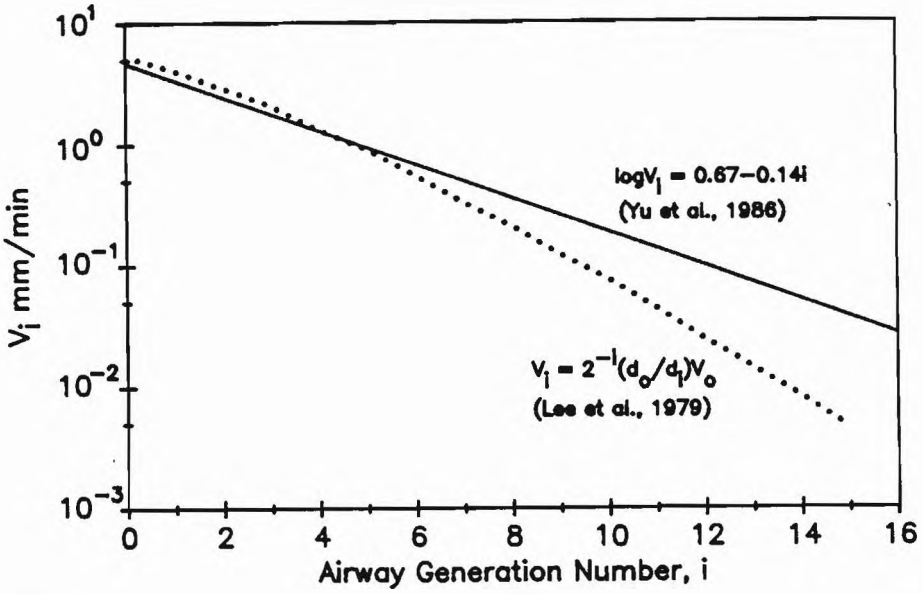
Describing tracheobronchial clearance by several clearance rates may have a physiological basis, since ciliary beat frequency increases from terminal bronchioles to trachea resulting in increasing velocities of the mucus (Iravani and van As, 1972). Indeed, Wilkey et al. (1980) estimated from studies in humans that bronchial clearance of inhaled 7.9 μm particles was fastest in the central zone, corresponding approximately to generations 1-6, and slowest for the peripheral zone, approximately generations 14-16. Respective retention

halftimes were 1.97 hrs, and 2.62 hrs. The intermediate zone in their experiment showed a slightly shorter retention halftime (1.70 hrs). Predicted clearance of inhaled 7.9 μm particles based on a tri-zonal clearance model proposed by the same group (Lee et al., 1979) agreed reasonably well with their experimental findings. Their mathematical model is based on Weibel's symmetric dichotomous lung model, additionally assuming that the mucous blanket which lines the airways is uniformly thick throughout the entire lung. Simulating in vivo conditions, transport rates of mucus decrease from trachea to terminal bronchioles in their model and gave the best agreement with experimental data when the velocity of mucus in the trachea was set at 5.5 mm/min, resulting in a velocity in the terminal bronchioles of 4.6 μm/min. The applied velocity for tracheal mucus is well within the range of rates measured experimentally with noninvasive radioaerosol boli techniques (Yeates et al., 1975). Transport velocities of tracheal mucus measured after intratracheal instillation of test particles in dogs were about 10 mm/min and in rats about 2 mm/min (Felicetti et al., 1981).

Yu et al. (1986) proposed a multicompartmental tracheobronchial deposition and clearance model by considering each airway generation as equivalent to an independent mucociliary escalator with its own length and transport velocity and interacting with the other escalators as a linked series. The resulting velocities of mucus are similar to the model by Lee et al. (1979) for trachea to generation 5, but are faster for the rest of the tracheobronchial tree with a velocity of the mucus in the terminal bronchioles of 30 μm/min (Fig. 3). Using their model, Yu et al. (1986) could improve the agreement between model prediction and the experimental result by Wilkey et al. (1980).

Both models predict the longest retention halftimes in zone III (generations 14-16) to be between 2 and 8 hours, apparently in agreement with the prevailing

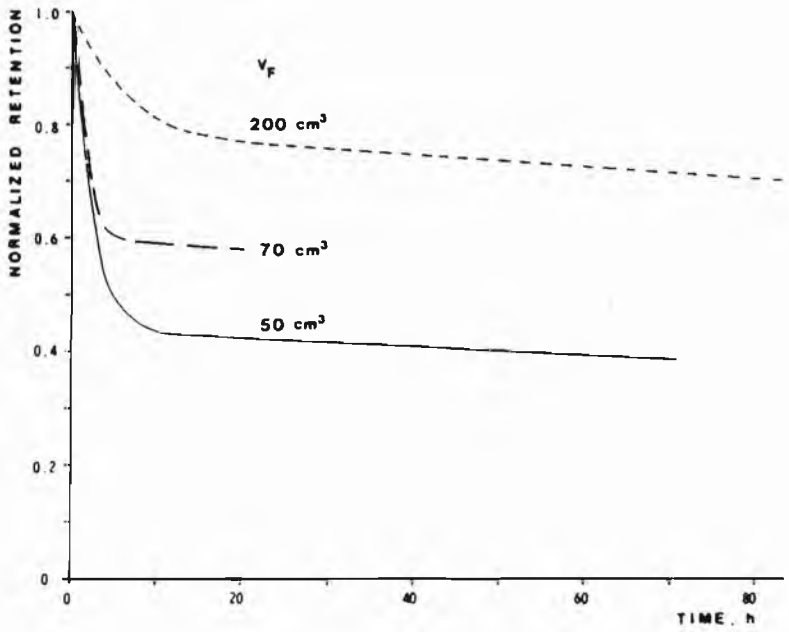
FIGURE 3
Mucociliary Escalator



Velocities of mucus in generations 0 (trachea) to 16 (terminal bronchioles) of human conducting airways were modeled by Yu et al. (1986) and Lee et al. (1979). Both models simulate reasonably well experimental results of mucociliary escalator mediated particle clearance from the tracheobronchial region (modified after Yu et al., 1986). V_o and d_o refer to the velocity of mucus and the diameter, respectively, of generation 0 (trachea), and V_i and d_i to velocity and diameter of the i-th generation.

view that tracheobronchially deposited particles are essentially all cleared within 24 hours. However, recent results by Stahlhofen et al. (1986) seem to suggest that a substantial portion of tracheobronchially-deposited particles may remain in the respiratory tract of humans beyond 24 hours: When a bolus of uniform 2.9 μm particles was inhaled with a breathholding maneuver to a volumetric depth in the lung of ~50 cm^3, i.e., corresponding to the upper generations of the respiratory tract, a significant retention of 40% of the deposited particles was observed beyond 24 hours (Fig. 4). This can be explained by either a much longer retention of particles in ciliated structures of the tracheobronchial tree or else by penetration of 40% of the particles into nonciliated airways due to mechanisms of flow-dynamics and distribution not yet understood (e.g., axial core flow, nonuniform asymmetric filling) - in which case postulation of extended tracheobronchial retention is not required. Although prolonged tracheobronchial retention of some particles could be explained by factors such as endocytosis of particles by epithelial cells, a discontinuous layer of the mucous blanket forming sites of inefficient clearance, or lack of a mucous epiphase in the bronchioles, the magnitude of the particles with prolonged retention (>40% of the deposited mass) is surprising and cannot easily be explained by such mechanisms. Retention due to particle phagocytosis by airway macrophages which adhere to epithelial cells underneath the mucous layer could possibly be a more likely explanation since the distribution of these cells along the airways with regard to surface area

FIGURE 4
Tracheobronchial Retention of Particles



Retention of 2.9 μm particles in human lower respiratory tract after their inhalation as boli to volumetric depth of 50, 70 and 200 cm^3 (Stahlhofen et al., 1986). Significant long-term retention beyond 24 hours occurred even after inhalation to volumetric depth of only 50 cm^3, presumably reaching the upper airway generations only. The retention of the radioactive tracer particles was measured by noninvasive external gamma-counting (courtesy of Dr. Stahlhofen). V_F is the depth of the aerosol pulse between larynx and the front of the aerosol bolus at end expiration, given in cm^3.

density is similar to that of the alveolar compartment (Lehnert and Sanz-Rodriguez, 1988). If such macrophage mediated particulate retention in the airways can be demonstrated these cells then may appear as inhibitors of a normally fast bronchial clearance. However, phagocytosis of particles (bacteria, antigens, etc.) by airway macrophages serves at the same time as a detoxifying and protective mechanism, as pointed out by Brain (1988). Smaldone et al. (1988) also reported significant retention of radioactively tagged particles presumably in central airways of humans at 24 hours post inhalation. They believe that the particles had failed to clear from central sites of initial deposition since the 24 hour retention pattern observed with a gamma camera correlated with the initial central deposition pattern. In addition, normal persons who deposited initially more in the periphery of the lung showed little retention in central airways at 24 hours so that movement of peripherally deposited material into central regions cannot account for a prolonged central retention (Smaldone et al., 1988). Further studies are required to examine the initial location and disposition of the deposited particles within the tracheobronchial tree to resolve the controversy of tracheobronchial retention beyond 24 hours. In a recent editorial, Foster (1988) dealt in more detail with the question of the 24 hour lung retention as an index of alveolar deposition. He concluded also that a more accurate assessment of aerosol deposition within central bronchi is needed to determine more precisely the effectiveness of mucociliary function within specific lung regions.

Several investigators have studied alterations of mucociliary clearance due to physiologic, pharmacologic or toxicologic stimuli. In general, as can be deduced from the preceding discussion, the rate of mucociliary clearance is a function of ciliary activity, the viscoelastic properties of mucus and of the site of deposition of the inhaled particles - which in turn depends on particle size, breathing parameters, and airway geometry. Changes in biochemical and physical properties of airway secretions and in vagal tone can affect the properties and thickness of mucus as well as the ciliary activity and mucociliary transport (Pavia, 1984). Table 1 summarizes factors known to alter mucociliary clearance.

TABLE 1
Factors Influencing Mucociliary Clearance

Increase	Decrease
Cough	Sleep
Physical exercise	Age
Inhalation of inocuous particles (high concentration, short duration)	Inhaled gases and particles:
SO_2	O_2;O_3(rat)
O_3 (man)	H_2SO_4;(high concentration)
H_2SO_4(low concentration)	cig. smoke (chronic)
Cig. smoking (initially)	Diseases:
Pharmaceuticals:	bronchitis
beta-adrenergics	bronchiectasis
cholinergics	asthma
aminophyllin	bronch. carcinoma
amiloride	cystic fibrosis (?)
mucolytics(?)	chronic flow limitation
histamine	primary dyskinesia syndrome
	Pharmaceuticals:
	anticholinergics (?)
	anesthetics
	aspirin

(Mossberg, 1980; Kenoyer et al., 1981; Matthys et al., 1983; Schlesinger et al., 1984; Pavia, 1984; Köhler et al., 1986; Smaldone, 1986; Foster et al., 1987). For more detailed information, see Pavia, 1984.

Insoluble Particles

As previously discussed (Fig. 1), the most efficient and prominent alveolar clearance mechanism for insoluble particles involves phagocytosis by alveolar macrophages (AM). AM are large mononuclear cells, representing more than 95-98% of the normal free cell population in the alveolar area. They originate from bone marrow precursor cells and are carried as monocytes to the lungs where they can mature and multiply in the lung interstitium (Pinkett et al., 1966; Brain et al., 1977; Blusse van Oud Alblas and van Furth, 1979; Johnson et al., 1980). AM can also multiply in the alveolar space (Blusse van Oud Alblas et al., 1983; Evans et al., 1986). Depending on the particle load in the alveoli after inhalation exposure, there can be an immediate influx of monocytes from blood into the alveoli followed by a delayed influx of macrophages from interstitial spaces (Adamson and Bowden, 1981). Endocytosis of particles by AM involves the recognition of the particle, adhesion and active phagocytosis (Ueda et al., 1981; Ito et al., 1981; Lehnert and Tech, 1985). A directed movement of AM to the site of deposition of particles and their subsequent phagocytosis by AM can be facilitated by chemotactic movement, probably involving activation of the complement cascade in serum by particles (Warheit et al., 1985, 1988). Although there is no evidence that this early chemotactically facilitated AM-particle encounter influences the long term AM mediated clearance of particles it may prevent free particles from entering the interstitium via endocytosis by epithelial cells. Phagocytosis of particles leads to metabolic activation of AM (respiratory burst) which in turn release a battery of mediators of different biological activities including oxygen metabolites, neutrophil chemotactic factors, lysosomal hydrolases, other proteinases, prostaglandins, plasminogen activators and fibroblast growth factors (Bitterman et al., 1982; Nathan, 1987). The rate of phagocytosis seems to depend on particle size, with an optimum size around 1.5-3 μm and a slower rate of phagocytosis occurring for smaller and for larger particles (Holma, 1967; Hahn et al., 1977).

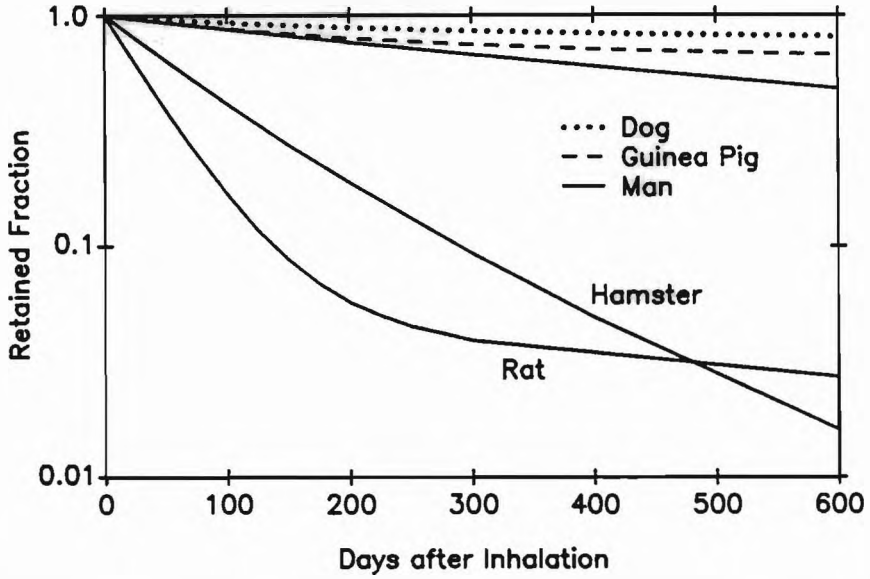
AM which have phagocytized particles will normally reach the mucociliary escalator, whether by random or by directed movement is not known. Investigation of clearance mechanisms of the transitional zone, i.e. the interaction of alveolar and mucociliary transport mechanisms, need certainly more attention. The old concept that AM can migrate back into the interstitium after phagocytosis of particles (Cummins and Sladden, 1930; Cole, 1944) was disputed by Lauweryns and Baert (1977) in their comprehensive review of alveolar clearance mechanisms and by Lehnert et al. (1986); however, this concept was recently revitalized by Harmsen et al. (1985) who found in dogs that after intrabronchial instillation of AM containing either green or red fluorescent microspheres that individual macrophages in regional lymphnodes contained almost only particles of one fluorescent color, rarely both. Thus, the possibility of alveolar clearance of particles within AM to regional lymphnodes should not be excluded but needs additional confirmation. Several authors suggested that AM which have entered the interstitium re-enter the airways at the level of the ciliated airways (Green, 1973; Tucker et al., 1973, Kilburn, 1974; Holt, 1982). However, unequivocal proof of such migratory behavior of particle laden macrophages is not available.

Free particles entering the interstitium can be carried to regional lymphnodes, entering the lymphatic capillaries through their intercellular clefts or after phagocytosis by the lymphatic endothelium (Lauweryns and Baert, 1977; Leak, 1980). There appears to be a limitation in diameter for particles which can be moved along those channels before they accumulate in the lymphnodes. For example, studies with 3-15 μm particles in rats and dogs indicate that 3 and 7 μm particles instilled into the lungs can be translocated to regional lymphnodes, but not 9-15 μm particles (Snipes and Clem, 1981; Snipes et al., 1984). It remains to be studied whether the limiting factor for transport of larger sized particles to lymphnodes lies in the transepithelial transfer or in the translocation within the lymphatic

channels. Penetration of particles through lymphnodes was reported in the early studies of Drinker et al. (1934), and from this and other studies (Ludwig, 1971) it appears that particles above 10 μm in diameter hardly penetrate the nodes. Even smaller particles of a few μm are retained to a high degree in the lymphnodes (Morrow, 1972), but some will penetrate them. Fibrous particles were also found to penetrate the lymphnodes and to appear in the postnodal lymph circulation, thus reaching the blood circulation (Oberdörster et al., 1988) and leading to a widespread systemic distribution (Godwin and Jagatic, 1970). Although the fraction of particles penetrating the lymphnodes is minor, it may become more important when a lung particulate burden is highly increased under conditions of high particulate exposures which subsequently increase particulate burden of the lymphnodes.

Ferin (1972) investigated the effect of the absolute lung burden of a dust on its removal rate. He found in this and other studies (Ferin, 1977), that high inhaled and instilled concentrations of TiO_2 particles in rats resulting in a high particulate burden of several mg/g lung led to a highly increased translocation of those supposedly innocuous particles to the thoracic lymphnodes. In addition, several investigators reported that at such high lung burdens of particles, alveolar clearance is severely retarded or can even cease completely (Ferin and Feldstein, 1978; Muhle et al., 1987; Bellmann et al., 1986; Wolff et al., 1987). This aspect will be discussed in more detail later. Measured pulmonary clearance rates due to mechanical clearance of highly insoluble particles (1-4 μm radiolabeled fused alumino-silicate particles) differ considerably in different animal species (Fig. 5). Respective retention halftimes range from about 50-100 days in rats, mice and hamsters to several hundred days in dogs, guinea pigs, and man (Bailey et al., 1985a,b; Snipes et al., 1983; Snipes and McClellan, 1985). It appears that mechanical lung clearance cannot always be described by monoexponential clearance kinetics, but can better be expressed as a multiphasic process. This is best illustrated by

FIGURE 5
Lung Clearance of Highly Insoluble Particles



Mechanical lung clearance of respirable radiolabeled fused alumino-silicate particles - excluding dissolution - was estimated in different species by pulmonary retention measurements over several hundred days (Snipes et al., 1983, 1985; Bailey et al., 1985a,b). Low in vivo dissolution of the particles was estimated from urinary excretion data of the label, and retention curves were adjusted for this in vivo dissolution.

results of Snipes et al. (1983) in rats (Fig. 5) which shows estimated mechanical clearance of inhaled ^{134}Cs-labeled fused aluminosilicate particles from retention measurements of up to 850 days. About 5% of the initial lung burden of a rat was estimated to be cleared mechanically with a long-term retention halftime of about 700 days, whereas the retention halftime for most of the pulmonary particulate burden changed with time from about 35 days during the first week after exposure to about 120 days after 6 months and to over 450 days after more than one year. A similar prolongation in retention halftimes in rats with time was reported by Bailey et al. (1985a), with halftimes of 32 days in the early phase of clearance and of 173 days after one year. Reported monophasic retention halftimes in rats of about 50-70 days for tracer particles in other studies (Ferin, 1978; Oberdörster et al., 1984; Lehnert and Morrow, 1985; Bellmann et al., 1986) might be due to the fact that clearance was followed only for 120 days or less by those investigators. As can be seen from Fig. 5, a constant clearance rate (monoexponential) with a corresponding retention halftime of about 60 days will very well describe the pulmonary retention characteristics of insoluble particles in the rat up to day 120.

Multiphasic alveolar clearance curves, although with different parameters and rates changing not as much as in the rat, were also found to fit observed data in dogs, guinea pigs, hamsters and mice (Snipes et al., 1983; Bailey et al., 1985a; Kreyling et al., 1986, 1988). Likewise, Bailey et al. (1985b) estimated from their studies in humans pulmonary mechanical clearance rates which changed with time (Fig. 6), starting at about 4 x 10^{-3} per day (equivalent to a retention halftime of about 170 days) and decreasing to a constant rate of about 1 x 10^{-3} per day (about 700 day retention halftime) at 300 days post inhalation. Since dissolution of the highly insoluble particles used in their study and subsequent absorption of the dissolved material was estimated to occur at rates approaching the mechanical long-term clearance rates, this was taken into account in those studies by measurement of in vitro solubility and in vivo urinary excretion rates. In addition, an estimated clearance due to transport into regional lymph nodes was considered in the calculations of Bailey et al. (1985). It appears that several hundred days after inhalation of even highly insoluble particles dissolution becomes a major clearance mechanism in the lung (Kreyling et al., 1988). However, lack of knowledge of exact in vivo dissolution rates and the possibility of chemical reactions of the dissolved labels in the lung are factors of uncertainty in the estimates of mechanical clearance rates.

Bohning et al. (1982) could describe effective clearance rates (including mechanical clearance and dissolution) of Sr-85-labeled polystyrene particles in normal humans by two exponential phases, with 27% of the particles being cleared with a corresponding retention halftime of 30 days and the rest with a halftime of 296 days. In their opinion, this suggests the existence of two different mechanisms of AM-mediated clearance, which could also be consistent with the data of Bailey et al. (1985b).

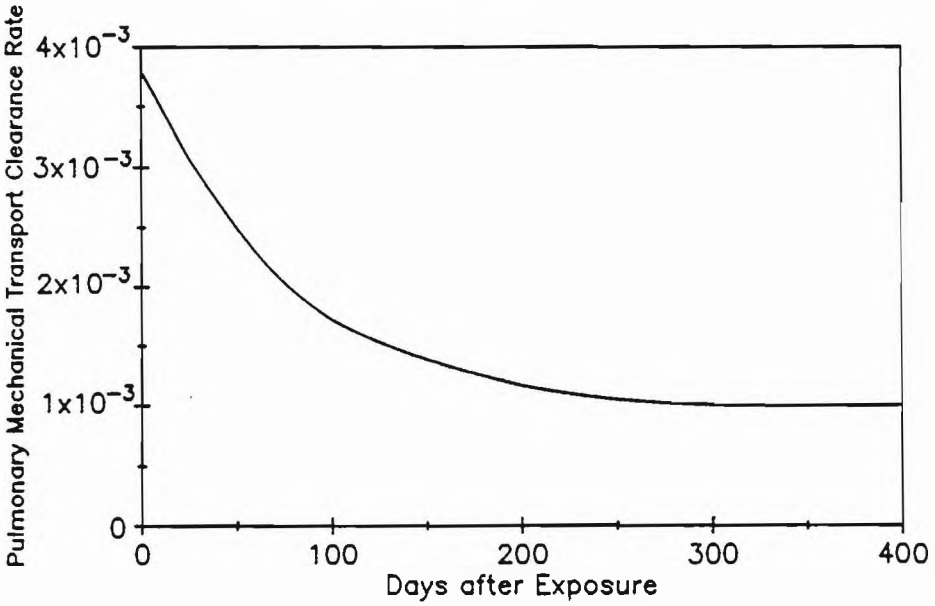
Based on the results of Bailey et al. (1985b) and similar results in humans with labeled teflon particles by Philipson et al. (1985), Cuddihy and Yeh (1988) proposed a mathematical model which makes use of variable clearance rates that are expressed in terms of the changing fractions of the remaining lung tissue burdens cleared per day. They suggested that the mechanical clearance rates for insoluble particles in man, M(t), vary with time according to:

$$M(t) = 0.005e^{-0.02t} + 0.001 \qquad (3)$$

(Cuddihy and Yeh, 1988). As one can see, at late time points after inhalation (>200 days) the clearance rate approaches a constant corresponding to a retention halftime of about 700 days (see also Fig. 6).

A comparison of retention data of different particulate materials (Bailey et al., 1985b) and the studies described in the preceding paragraph support the view that in a given animal species AM mediated clearance changes with time and is independent of the particulate compound as long as the compound exhibits very low in vivo solubility and cytotoxicity. Results of some other studies do not seem to fit this concept. For example, studies in rats, dogs and humans with inhaled metallic iron, Fe_2O_3, Fe_3O_4, UO_2 or soot particles showed a

FIGURE 6
Alveolar Mechanical Clearance Rates



Fractions of 1 and 4 μm labeled fused alumino-silicate particles cleared daily from the pulmonary region of the human lung were estimated after correction for dissolution and transport to lymph nodes (after Bailey et al., 1985b). A slightly slower mechanical clearance rate estimated for the 1 μm particles up to day 100 and a slightly slower clearance rate for 4 μm particles beyond day 200 was found; yet, in view of the uncertainties in the estimated dissolution rates, these differences were not regarded as significant by the authors (Bailey et al., 1985b). Thus, an averaged clearance rate for both particles is shown in this figure. Fractional dissolution rates for these particles in the human lung were estimated from urinary excretion of the label as 6.9×10^{-4} per day for 1 μm particles and as 2.2×10^{-4} per day for 4 μm particles; fractional mechanical transport to lymph nodes was assumed to be 3.5×10^{-4} per day as proposed by the International Commission on Radiological Protection (ICRP, 1966), which is in the same range as values of $1 - 2 \times 10^{-4}$ per day estimated for this translocation pathway from dog studies.

pulmonary retention halftime in all three species of about 60-100 days (Albert and Arnett, 1955; LaBelle and Brieger, 1961; Gibb and Morrow, 1962; Cohen et al., 1979; Chan et al., 1984). However, it is not known to what extent particle dissolution contributed to these retention halftimes; in addition, the length of the observation period may not have been long enough to determine a longer retention halftime as discussed above. Other studies with inhaled UO_2 particles showed a high correlation of pulmonary clearance rates in rats even with low UO_2 lung burden (Downs et al., 1967). Whether AM function was affected by the low UO_2 lung burdens (45-410 μg/g lung) is not known, however, no pathological effects in the lungs were observed. Possibly, AM mediated clearance is specific for some particulate compounds of very low toxicity and of low in vivo solubility thus making it difficult to apply a common mechanical pulmonary clearance rate to all particles of this kind.

The clearance kinetics discussed above were observed after a single inhalation exposure to particles of low toxicity (biologically "inert") leading

to a low particulate lung burden of a few micrograms per gram lung tissue. However, for biologically active (or toxic) particles - e.g., silica - lung clearance could be quite different. Additionally, effects of such toxic particles on AM could lead to an impairment of lung clearance of other "inert" particles, as demonstrated by the prolongation of Fe_2O_3 particle ("inert") clearance after long-term exposure to low concentrations of NiO and CdO (toxic) aerosols was observed (Oberdörster and Hochrainer, 1980a,b).

As mentioned before, exposure even to so called "inert" or "nuisance" particles at high concentrations resulting in lung burdens in the mg/g lung tissue range can lead to significant retardation or even to stasis of particulate lung clearance. For example, it was reported that the elimination of particles from the alveolar compartment was decreased in rats exposed chronically to high concentrations of TiO_2 particles (Bellmann et al., 1986; Muhle et al., 1988). The inability of AM to eliminate the deposited particles resulted in a much higher lung burden of inhaled TiO_2 particles than predicted from retention data derived from lower levels of exposure. Concurrently, redistribution of particles into interstitium and lymphatic tissue was also found, confirming earlier results by Ferin (1977) that a high particulate lung burden will lead to an increased accumulation of particles in regional lymph nodes. As evidenced by many long-term studies in rats in which different dust materials were used, e.g., TiO_2, coal dust, carbon particles, fly ash, PVC particles, diesel particles, photocopier toner particles, SiO_2 and asbestos (Le Bouffant, 1971; Ferin, 1972; Davis et al., 1978; Bolton et al., 1983; Wehner et al., 1983; Chan et al., 1984; Bellmann et al., 1986; Wolff et al., 1987; Lee et al., 1987; Muhle et al., 1987, 1988), the prolongation of dust retention in the lungs of laboratory animals exposed for many months to high dust exposure levels appears to be a nonspecific phenomenon seen with many different kinds of particles including so-called biologically "inert" dusts. Impaired particle clearance was typically accompanied by an inflammatory response in the respiratory tract, macrophage recruitment and epithelial cell proliferation.

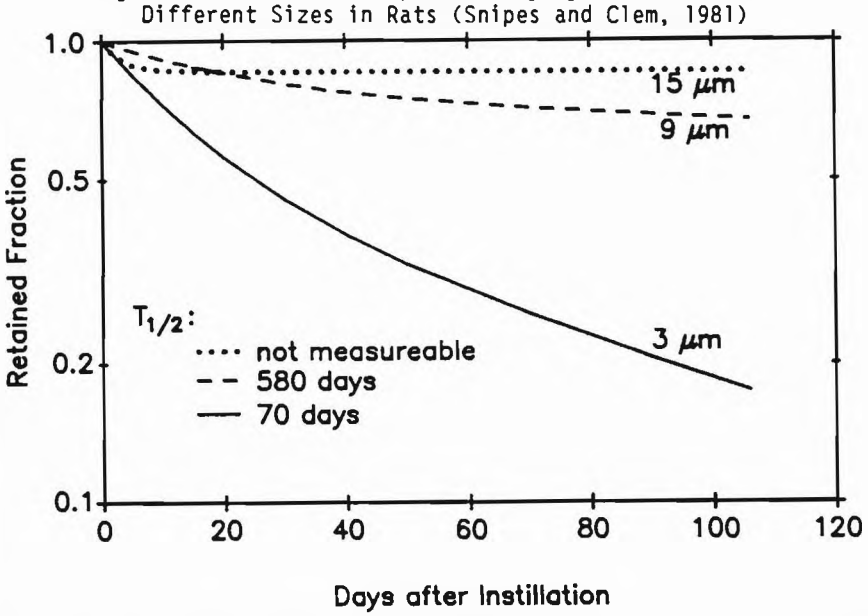
From such observations of nonspecific inhibition of pulmonary clearance mechanisms the concept of the "overloading" of the pulmonary clearance has emerged, i.e., the accumulation and persistence of excessive amounts of a non-biodegradable particulate material in the lung retards lung clearance and eventually induces lung injury. This includes - in addition to inflammatory reactions and macrophage aggregations - the development of fibrotic changes and even lung tumors (Campbell, 1937; Martin et al., 1977; McClellan et al., 1986; Heinrich et al., 1986; Vostal, 1986; Lee et al., 1985). This concept of overload implies that biologically "inert" particles do not exist, but that any particle at sufficiently high lung burdens will eventually cause lung damage. Underlying biochemical mechanisms of damage include the release of mediators from activated AM and chemotactically recruited neutrophils affecting tissue functions (e.g., released oxygen metabolites affecting alveolar membrane integrity; Welsh et al., 1986; Pitt et al., 1987). It appears, that a threshold concentration of the dust in the lungs exists above which the effects of "overloading" occurs, and this concentration seems to be above 1 mg of dust per gram lung tissue (Bolton et al., 1983; Morrow and Mermelstein, 1988), possibly as high as 2 or 3 mg/g.

Although high dust loads of "inert" particles in the alveolar space lead to adaptive responses including influx of blood-borne macrophages and neutrophils (early phase) and of proliferating interstitial macrophages (later phase) into the alveoli (Adamson and Bowden, 1981), physical "overloading" of the individual macrophages may eventually occur when they are no longer able to cope with the high dust burden, and the dust clearance function subsides (Bowden, 1987). Lauweryns and Baert (1977) described this as AM reaching an exhaustion stage dependent on the maximal capacity of the plasmalemma, and they report a value of 50% of the cell membrane to be capable of incorporating ingested particles (Chapman-Andresen, 1963, cited in Lauweryns and Baert, 1977).

Recently, Morrow (1988) hypothesized that it is the volume of the phagocytized particles per AM rather than the mass burden per gram lung which inhibits AM function under conditions of "overload". According to this hypothesis, a maximum phagocytized volume would incapacitate AM movement.

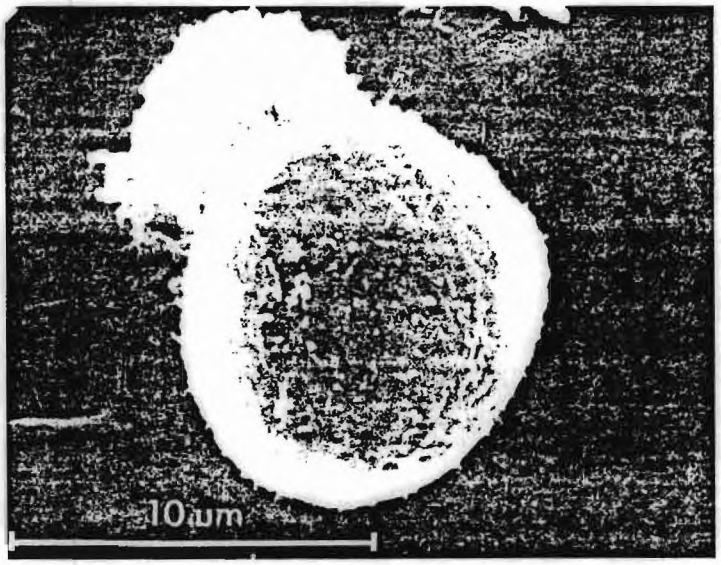
Morrow (1988) described this as the "volumetric limit" of the AM in his detailed discussion on dust overloading mechanisms. He suggested that this volume is about 60% of the normal macrophage volume which leaves the AM functionally impaired, a value which he estimated from published data on AM recruitment, lung dust burdens and dust clearance. Considering a normal volume of a rat AM of about 1000 μm^3 (Lehnert and Morrow, 1984), this would mean that phagocytosis of 74 particles with a diameter of 2.5 µm by a single AM could lead to its volumetric overloading. Alternatively, one single phagocytized particle of 10.5 µm diameter would also result in volumetric overloading. Indeed, Snipes and Clem (1981) found in rats that the pulmonary retention halftimes ($T_{1/2}$) increased significantly for large particles even at low particulate lung burdens (Fig. 7): Whereas a normal $T_{1/2}$ of 70 days was determined for 3 µm particles, it increased to 580 days for 9 µm particles and was not measurable for 15 µm particles over the observation period of 106 days. Similar results were obtained in dogs where the normal retention halftime of 820 days for 3 µm particles increased to very long retention halftimes not measurable over a 120 day period for 7 and 13 µm particles (Snipes et al., 1984). No proof was provided that the bigger particles were actually phagocytized by AM. However, we could demonstrate in a recent pilot experiment in rats (unpublished results) that 10.3 µm polystyrene particles were readily phagocytized by AM (Fig. 8). It is easily conceivable that AM filled with a phagocytized particle volume as shown in Figure 8 will be highly immobile: the normally ruffled surface is stretched smoothly and seems hardly capable of forming pseudopodia or of engulfing additional particles. Rheologic cell properties such as cytoplasmic viscosity and elasticity important for AM function (Valberg and Feldman, 1987) might also be disturbed resulting in

FIGURE 7
Lung Clearance of Monodispersed Polystyrene Particles of Different Sizes in Rats (Snipes and Clem, 1981)



The particles had been instilled intratracheally as a mixture of all three sizes (50 µg of ^{141}Ce labeled 3 µm particles; 5 µg of ^{85}Sr labeled 9 µm particles and 2 µg of ^{46}Sc labeled 15 µm particles) on day 0, and subsequent pulmonary retention was followed for up to 106 days for determination of the retention halftimes. The label of the 3µm particles only was found in the lung associated lymphnodes, indicating a size limitation for particlate translocation either across the alveolar epithelium or within pulmonary lymphatic vessels.

FIGURE 8
Alveolar Macrophage in Broncho-Alveolar Lavage of a Rat with Phagocytized 10.3 μm Polystyrene Particle



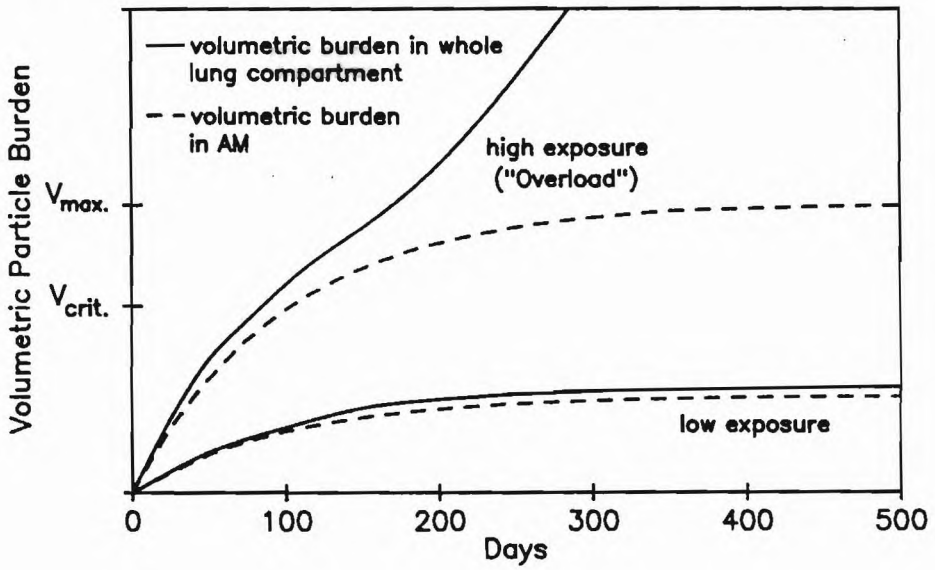
The monodispersed 10.3 μm particles had been instilled intratracheally 24 hr prior to the broncho-alveolar lavage. Almost all of them were found to be phagocytized by AM. Cells were fixed in 2% glutaraldehyde in 0.1 m phosphate buffer and prepared for SEM.

a disruption of the cytoskeleton. Possibly, in less extreme cases as that shown in Fig. 8 – i.e., with many small particles instead of one big particle – disturbances of AM fluidity may not be as severe.

So far, the phenomenon of chronic particle overload has only been reported in experiments with rats in which high air concentrations (>5 mg/m^3) of inert particles inhaled over weeks and months resulted in a significant reduction of AM mediated particulate clearance and eventually fibrotic lung disease. Many questions remain unanswered at this point, e.g., is the loss in AM function reversible? Does the initial adaptive increase in AM numbers seen in acute overload situations (Adamson and Bowden, 1978) persist in chronic overload conditions? What is the significance of the dust deposition rate vs. the total lung dust burden? Is there a common pathogenetic mechanism of chronic interstitial lung disease caused by overloading with low toxicity dust and by lower lung loads of cytotoxic dust? and finally: what are the implications for human exposure to high dust levels? Answers to such questions will not only shed light on mechanisms involved in overload situations but are also important for the understanding of basic clearance mechanisms and the pathogenesis of lung diseases. For example, Rom et al. (1987) and Bowden (1987) discuss the central role of activated AM in the pathogenesis of pneumoconioses after chronic exposure to high concentrations of inorganic dusts since they found under such exposure conditions an increased release from AM of AM derived growth factor and fibronectin which are important for fibroblast attraction and replication.

Predicted kinetics of dust retention in the lungs during chronic high exposure conditions are shown in Figure 9 for a rat lung based on the experimental findings of several groups (Chan et al., 1984; Bellmann et al., 1986; Wolff et al., 1987; Muhle et al., 1988). At low to moderate exposure

FIGURE 9
Particle Accumulation in the Lung During Normal and Impaired Clearance



The kinetics of particle accumulation in the lungs of rats during chronic low and high exposure concentrations of "nuisance" particles are derived from results of Chan et al. (1984), Bellmann et al. (1986), Wolff et al. (1987) and Muhle et al. (1988). The particle burden is expressed as volumetric particle burden since this seems to correlate with AM mobility (Morrow, 1988). Particulate burden in whole lung compartment reflects particles in AM, free particles in the alveolar epithelium and particles in the pulmonary lymph nodes. At low exposure concentrations, the particulate burdens in the lung and AM reach a steady state, which can be predicted by the daily deposition and clearance rates according to: $V_t = V_D/k \cdot [1-(\exp-kt)]$, where V_t = accumulated particle volume at time t; V_D = daily deposited volumetric particle burden; k = alveolar clearance rate. At high exposure concentrations, when a critical volume (V_{crit}) of phagocytized particles is reached, AM mediated particle clearance begins to slow and accumulation of particles in the lung increases. At the maximum phagocytized volume (V_{max}), AM mediated particle clearance is predicted to subside and the rate of accumulation of particles in the lung may become equivalent to their deposition rate.

concentrations of particles, the lung burden - here expressed as volumetric lung or AM burden - will reach an equilibrium when the pulmonary clearance rate is equivalent to the pulmonary deposition rate, i.e., after about 12 months in the rat. However, during chronic high exposure concentrations when AM particle burdens have reached a critical value, normal AM mediated clearance begins to be impaired and eventually may cease when a maximum phagocytized volume ("volumetric limit") of particles is reached in the AM (Morrow, 1988). Particle accumulation in the lung then does not follow the predicted pattern but may eventually become linear reflecting the deposition rate of the inhaled particles. Muhle et al. (1988) determined empirically that the pulmonary clearance rate of particles decreased linearly with the logarithm of particulate mass in the lung once a critical mass burden had been reached.

Although the existence of such overload related impaired lung clearance of particles has not been demonstrated in humans it is probably not restricted to rats as can be deduced from the previously mentioned retention studies with large particles in dogs of Snipes et al. (1984). Furthermore, Muhle (1988)

observed in hamsters an impairment of particle clearance after exposure to high concentrations of photocopier-toner particles. It is conceivable, therefore, that humans occupationally exposed to high dust concentrations on a chronic basis might show signs of "overload" related impaired particle clearance and lung damage (Bowden, 1987). For example, it is well known from studies in coal miners that exposure to excessive amounts of respirable coal mine dust will lead to an increased risk of progressive massive fibrosis, chronic bronchitis or emphysema (Ruckley et al., 1984; Miller and Jacobsen, 1985; Rom et al., 1987). In earlier studies, Nagelschmidt (1965) reported that in coal workers extremely high amounts of lung dust of 9 g to over 60 g correlated with the severity of pulmonary fibrosis. However, they pointed out in addition that the rank of the coal is of importance for its fibrogenic potential. It is intriguing to view this response to chronically-inhaled high levels of coal dust as a consequence of dust overloading of AM mediated clearance in humans - analogous to results of rat studies. Indeed, Freedman and Robinson (1988) found in coal workers a decreased clearance of the inhaled coal dust as one indicator of an effect of chronic exposure. The demonstrated importance of coal rank for the fibrogenic response may indicate that cytotoxicity of the different coal dusts could also play a role. In contrast to the coal dust, much lower amounts of lung dusts of 2-6 g in fibrotic coal workers' lungs were found when 30-50% of the retained dust consisted of the more cytotoxic quartz particles (Nagelschmidt, 1965).

In view of the results of the animal experiments it is therefore prudent not to exclude the possibility of dust overload effects in humans. Considering a recommended threshold limit value (TLV) in the U.S. for occupational exposure to so-called "nuisance dust" of 10 mg/m^3 (ACGIH, 1987), a chronic eight hour daily exposure to this permissible level could lead to dust accumulation of several mg dust per gram lung.[1] This should alert us to an important issue in occupational health which calls for further attention and re-evaluation of present nuisance dust standards by health authorities.

Figure 10 depicts a compartmental scheme of particle translocation in the peripheral lung region under conditions of normal low exposure concentrations and high exposure concentrations (overload). Differences in translocation pathways, relative translocated amounts and translocation rates between "normal" and "overload" are indicated as well as gaps in our knowledge for such translocations. The scheme is simplified in several respects: Particles in interstitium and lymph nodes are placed into the same compartment as representing a common pool of particles which have crossed the alveolar membrane. Obviously, biological consequences are quite different whether particles are in the interstitium or in lymph nodes. It is assumed, that released particles from dying AM (k_2) will be taken up by other AM under normal conditions (k_1) - a repeatedly described concept (Heppleston, 1963; Heppleston and Young, 1973; Lehnert et al., 1986) which is supported by recent studies of Lehnert et al. (1988) - whereas they remain mostly in the free particle pool under conditions of overload. Based on the suggested immobility of overloaded AM it is further assumed that overloaded AM do not transfer into the interstitium (k_4) but that the reported interstitial dust accumulation occurs via the free particle pool (k_3) (Lehnert et al., 1986; Bowden, 1987). Clearly, more studies are needed to elucidate the mechanism of interstitial dust accumulation in overload situations. The scheme also simplifies by

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[1] Assuming (1) these are respirable particles (mass median aerodynamic diameter = 3.5 μm with geometric standard deviation of 1.5); (2) a (conservatively low) pulmonary deposition of 15%; (3) an inhaled volume of 10 m^3 per day; (4) a pulmonary retention halftime of 500 days; and (5) a human lung weight of 950 g), the accumulated dust concentration in the lung would reach a steady state of 11 mg dust per gram lung, a level which is known from rat studies to cause lung damage due to overload as discussed in the preceding paragraphs. Even the legal OSHA standard in the U.S. of 5 mg/m^3 respirable particles could lead to lung dust accumulation of over 5 mg/g which is still an excessive level.

showing the same designation for slow clearance processes of AM containing particles (k_6) for normal and overload conditions; yet, this pathway represents more than one clearance mechanism which are very likely different under normal and overload conditions, i.e., active movement of AM and passive movement due to fluid fluxes. An adaptive increase in AM numbers under chronic overload conditions - as suggested in Fig. 10 - may reasonably be assumed from acute high particle load studies (Brain, 1971; Adamson and Bowden, 1978, 1980; Bowden, 1987) unless the interstitial macrophage pool and/or blood monocytes become exhausted and cannot replenish AM at the same rate at which they are dying. This seems, however, unlikely since Strom (1984) and Henderson et al. (1988) found that after two years of exposure of rats to high concentrations of diesel exhaust the numbers of lavagable AM were doubled compared to controls.

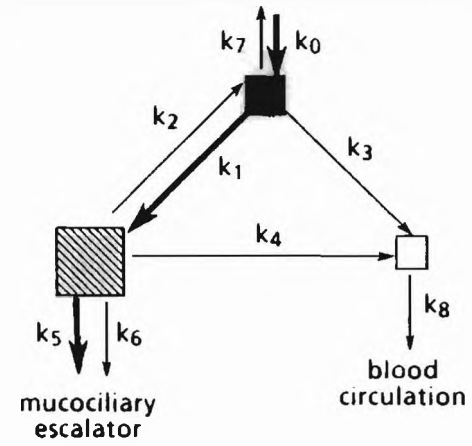
In an attempt to model overload related clearance phenomena, Yu and Morrow (1986) created a nonlinear mathematical model in which the clearance rate is a function of mass burden in the lung and which could describe increasing pulmonary particle accumulation observed in rat studies with high exposure concentrations. Likewise, the nonlinear sequestration model by Chan et al. (1984) and Strom and Chan (1988) provides a description of overload effects by introducing a sequestration compartment - represented by aggregated AM - with a very long retention halftime. Introduction of a "sequestration" compartment (Bolton et al., 1983) could accommodate both a prolonged long-term retention of a small fraction of particles observed under normal conditions (Fig. 5) and the prolonged retention under overload conditions. The anatomical correlate of the sequestration compartment in overload situations might be the so-called "dust plaques" (Gross and Hatch, 1962) which could be considered as a reservoir from which particles are liberated into the alveolar interstitium (Lauweryns and Baert, 1977).

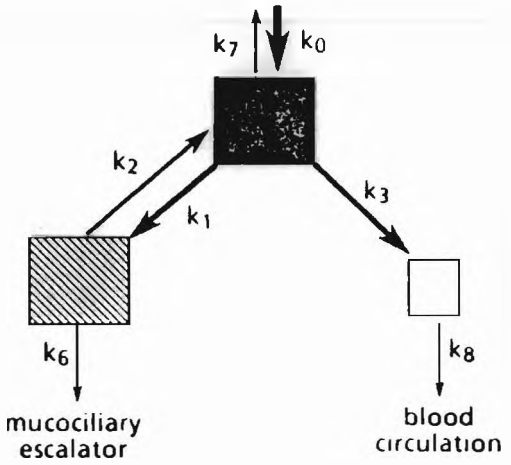
Most recently, Stöber (1988) proposed a multicompartmental alveolar clearance model for insoluble particles which takes into account physiologic mechanistic features such as AM lifetime, decreasing macrophage mediated transfer rates with increasing lung dust burden, and particle release from dying AM with subsequent re-phagocytosis from the epithelial surface. The quantification of this latter transfer rate with all its consequences was first introduced into a model by Stöber (1988) who termed it "reverse transfer rate." This model may give reasonable predictions of both particle accumulation during normal and excessive loading and subsequent clearance or irreversible retention after exposure cessation. A different model incorporating particle deposition as well as the different aspects of particle clearance discussed in this section was recently described by Smith (1985). This model features clearance rates which change with dust load due to a biological feedback system; it assumes saturable Michaelis-Menten kinetics for uptake of particles into AM as described by Biozzi et al. (1953) and takes into account dissolution of particles. The possibility of clearance of free particles as well as particle sequestration within the interstitial compartment are also included. Although this model was specifically developed for describing the clearance kinetics of quartz particles and the related development of fibrosis, its parameters are easily adjustable to new data as they become available to model pulmonary clearance kinetics of particles of low cytotoxicity. However, these useful modeling attempts should not distract from the necessity that more kinetic and mechanistic experimental studies and data on AM behavior and function under normal and overload conditions are needed to understand the pathogenetic consequences.

Soluble Particles (Solutes)

The alveolar-capillary membrane is extremely well endowed to fulfill a number of different physiological tasks. Besides its function of efficiently exchanging oxygen and carbon dioxide, it also provides transport of macromolecules in both directions. Two major physiological functions, in addition, are the formation of a barrier against the penetration of harmful airborne particulate matter after deposition in the alveolar compartment and the prevention of leakage of solutes from capillaries into alveolar spaces.

Fig. 10: Translocation of highly insoluble particulate material of low cytotoxicity in the distal lung during chronic exposure to low (normal) and very high (overload) particle concentrations in the air.





Low particulate exposure
Particulate burden in lung reaches steady state and is nearly equivalent to AM particulate burden **(normal)**

High particulate exposure
Particulate burden in AM reaches steady state; particle build up in lung continues with exposure **(overload)**

free particle pool

particles in resident and newly arrived AM

particles in interstitium and lymph nodes

The scheme is complicated by the appearance of numerous PMN in overload conditions which also phagocytize particles yet have a much shorter life span in the alveolar space than AM. In addition, release of mediators from activated AM and PMN affects function of these cells and of the epithelial barrier. Dissolution of particles can also play a role, and the dissolution rate depends on the particulate material and on whether it is located in AM, on the epithelium or in the interstitium.

Translocation Pathway		Mechanism of Translocation	Flux of Particulate Mass		Fractional Transfer Rate in Overload Compared to Normal
			Normal	Overload	
Input	k_0	deposition of inhaled particles	low	high	no change unless change in

particles yet have a much shorter life span in the alv[illegible]r space than AM. In addition, release of mediators from activated AM and PMN affects functi[illegible]of these cells and of the epithelial barrier. Dissolution of particles can also play a role, and the dissolution rate depends on the particulate material and on whether it is located in AM, on the epithelium or in the interstitium.

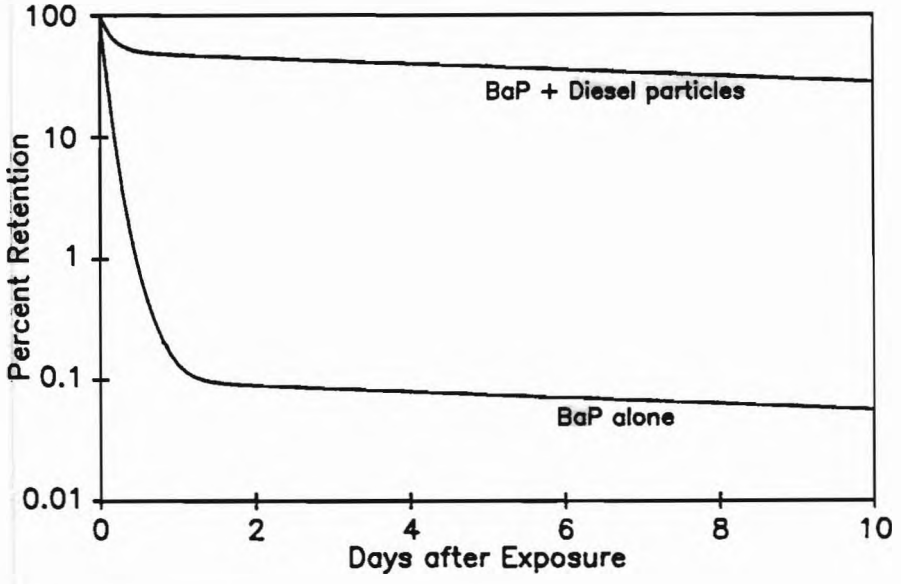
Translocation Pathway		Mechanism of Translocation	Flux of Particulate Mass		Fractional Transfer Rate in Overload Compared to Normal
			Normal	Overload	
Input	k_0	deposition of inhaled particles on alveolar epithelium	low	high	no change unless change in lung structure or respiration
Intrapulmonary translocation	k_1	phagocytosis of free particles by resident AM	low	high	lower
	k_2	release of particles from dying AM into free particle pool	low	high	higher
	k_3	transepithelial transport of free particles into interstitium and lymph nodes	very low	high	no change (?)
	k_4	migration of AM containing particles into interstitium and lymph nodes	low	none (?)	lower
Output	k_5	fast clearance of mobile AM via mucociliary escalator	high	none	lower
	k_6	slow clearance of AM via mucociliary escalator	low	low	lower
	k_7	removal of free particles via mucociliary escalator	very low	low (?)	no change (?)
	k_8	postnodal clearance of particles from lymph nodes	low	low (?)	lower (?)

Thus, the integrity of the alveolar-epithelial barrier is important for several physiological functions.

Inhaled aerosolized soluble compounds which are deposited in the alveolar region are mainly cleared into the interstitium via transepithelial transport (Fig. 1). This transport and the resulting pulmonary retention of these compounds are influenced by their water or lipid solubility, their molecular size and by chemical reactions (e.g., binding to proteins, cell structures) in the lung. Absorption studies with non-reacting lipid-soluble and water soluble solutes showed that they are absorbed from alveoli by diffusion across a lipoid-pore membrane (Taylor and Gaar, 1970; Enna and Schanker, 1972). Lipid soluble substances of diverse chemical structure and degree of ionization penetrate the alveolar epithelium at rates which increase roughly with their lipid water partition coefficient, passing easily through the bilipid cell-membrane rather than the intercellular junctions (Jones et al., 1982). Since this is a very rapid process the clearance rate of lipophilic compounds from the alveolar space is limited mainly by blood perfusion which needs to be sufficiently high to maintain a concentration gradient.

However, pulmonary retention of lipophilic compounds, and possibly hydrophilic compounds, can markedly be increased by adsorption onto particles. For example, adsorption of benzo-a-pyrene (BaP) onto inhaled diesel particles increased the pulmonary retention of BaP one day after inhalation from about 1%, when BaP was inhaled alone, to about 50% when it was adsorbed onto inhaled diesel particles (Bond et al., 1986) (Fig. 11). Since this longer retention means a prolonged exposure of lung target cells to BaP, it may conceivably augment the adverse effect of this carcinogen as suggested by Saffiotti et al. (1968). In general, the prolongation of pulmonary retention of the solute

FIGURE 11
Effect of Particles on Lung Retention



Pulmonary retention of a lipophilic organic compound (Benzo-a-pyrene, BaP) is altered depending on whether it is inhaled alone or adsorbed onto inhaled diesel particles (after Bond et al., 1986). Although the initial dose rate of BaP delivered to target cells on day one is much higher when the compound is inhaled alone, adsorption onto the particles results in a higher dose delivered daily to target cells after day one. Since diesel particles are phagocytized by AM the prolonged retention reflects either BaP still on the particles or retention of BaP after desorption from the particles in AM.

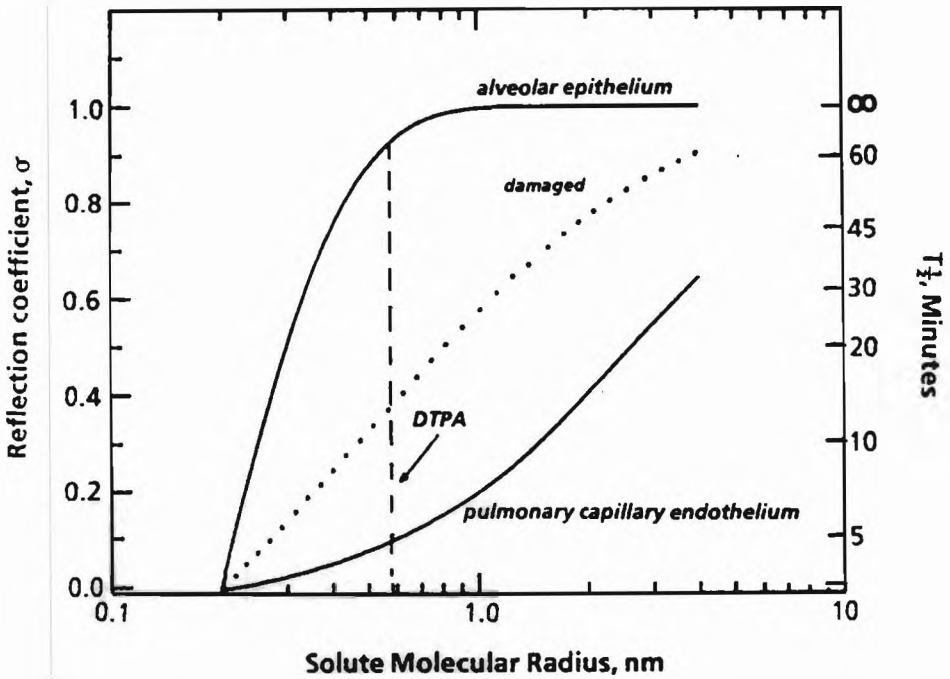
adsorbed onto particles depends on the physico-chemical nature of both the particles and the adsorbed compound (Bond et al., 1986). Such physical interactions and resulting physiological consequences may have practical implications for effects of compounds adsorbed onto particles in cigarette smoke and in the urban and occupational environment. Likewise, physico-chemical reactions of inhaled gaseous compounds with particles could enhance the effects of the gaseous substance due to a carrier effect. For example, inhaled SO_2, which is normally effectively absorbed in the nasopharyngeal region, can penetrate the upper airways when it is absorbed into and reacts with a wet aerosol (McJilton et al., 1976).

In contrast to lipophilic solutes, clearance of hydrophilic solutes is limited by their diffusion rate. Several investigators have determined "effective" pore sizes for water soluble substances in both the alveolar epithelial and the capillary endothelial layer by using macromolecules and lower molecular weight solutes given intratracheally or intravenously under normal and altered physiological conditions (Taylor et al., 1965; Taylor and Gaar, 1970; Enna and Schanker, 1972; Schneeberger, 1976; Jones et al., 1978; Nelson, 1978; Gardiner, 1978; Egan, 1980). From results of such studies it was derived that pore sizes of the alveolar epithelium are in the range of 0.6-1.5 nm and those of the endothelium in the range of 2-13 nm. The concept of pores assumes that hydrophilic solutes of low molecular weight deposited in the lung by inhalation will diffuse through the alveolar epithelium and capillary endothelium via these pores, whose anatomical correlate is thought to lie in the region of the intercellular tight junctions (Schneeberger and Karnovsky, 1976; Chopra et al., 1979; Jones et al., 1982; Effros and Mason, 1983). The molecular size of the hydrophilic solutes deposited in the lung represents the rate limiting factor for diffusional clearance of those solutes from the lung, and an inverse relationship between clearance rate and solute molecular weight exists (Effros and Mason, 1983). In addition to these diffusional processes via intercellular tight junctions, transcellular transport of solutes by pinocytotic activity in epithelial cells occurs (Chinard, 1980). This is particularly important for larger solute molecules, such as proteins, for which intercellular junctions are highly impermeable. An increased transfer by this transcellular route was reported following epithelial damage in the tracheobronchial and alveolar region after O_3 exposure (Bhalla and Crocker, 1986, 1987).

Reflection coefficients as a measure of osmotic effectiveness can be used to describe hydrophilic solute permeability across the alveolar-endothelial barrier, i.e., a reflection coefficient of 0 means a freely permeable membrane and a reflection coefficient of 1 represents an ideal semipermeable membrane, permeable for the solvent, but not the solute. Figure 12 shows schematically the correlation between reflection coefficients for alveolar epithelium and pulmonary capillary endothelium for different molecular solute radii. It shows, that the permeability properties of the alveolar capillary membrane to hydrophilic solutes is determined primarily by the alveolar epithelium rather than the capillary endothelium. Corresponding permeability coefficients for the pulmonary capillary endothelium are approximately 10 times greater than for the alveolar epithelium (Staub, 1974). Thus, the alveolar epithelium, in contrast to the capillary endothelium, is only slightly permeable to hydrophilic solutes with molecular weights above 15000 daltons and essentially impermeable to molecules above 40,000 daltons (Jones et al., 1982). Several workers suggested that the normal alveolar barrier is completely impermeable to protein (Egan et al., 1977; Nelson et al., 1978; Egan, 1982) like in the fetal lung (Adams, 1966). Physiologically, however, a finite permeability for protein is present, and the results of several studies in dogs showed an average clearance rate for protein of 1% per hour (Staub, 1983). Pinocytotic transport may contribute to this rate, as mentioned above.

Based on these physiological principles of epithelial permeability, a noninvasive method of determining the integrity of the alveolar epithelium with inhaled hydrophilic solutes has been developed. The technique makes use of the measurement of the pulmonary clearance rate of a small molecular weight tracer, ^{99m}Tc-labeled diethylenetriaminepentaacetic acid (DTPA), a stable chelator

FIGURE 12
Reflection Coefficients of Alveolar Epithelium and
Pulmonary Capillary Endothelium for Hydrophilic Solutes



The molecular radius for $NaCl_2$ is ~0.23 nm, for albumin ~3.6 nm (modified after Jones et al., 1982). The reflection coefficient is the ratio of the actual osmotic pressure and the ideal osmotic pressure for a given concentration of the solute: A reflection coefficient of 1 represents an ideal semipermeable membrane, and of 0 a freely permeable membrane. The alveolar retention halftimes, T1/2, shown for the solute diethylenetriaminepentaacetic acid (DTPA) with a molecular radius of 0.57 nm, indicate a value of about 60 min for the normal alveolar epithelium which will decrease substantially for the damaged alveolar epithelium, shown here as a hypothetical dotted line. In theory, the alveolar epithelium could be damaged to a degree that solute clearance becomes limited by the endothelial barrier of the pulmonary capillaries, provided, the capillary endothelium remains unaltered in such situations.

(Chopra et al., 1979; Rinderknecht et al., 1980; Jones et al., 1982; Coates and O'Brodovich, 1986). As pointed out by Effros and Mason (1983), it is necessary that solutes used in this method, like DTPA, do not react or bind to specific sites or cross actively the epithelial membrane. This tracer is inhaled as an aerosol of submicronic particles so that they are deposited primarily in the alveolar region of the lung. Upon deposition of the solute droplets, they merge with the fluid lining the alveolar surface, a process which is possibly influenced by surface tension. The molecular size of DTPA of 492 daltons corresponds to a molecular radius of 0.57 nm (Jones et al., 1982) and thus DTPA can easily penetrate the endothelial layer (Fig. 12). However, if unaltered, the tight alveolar epithelium represents a barrier to DTPA diffusion so that its clearance occurs at a rate corresponding to a halftime of about 60-85 minutes in humans (Mason et al., 1985; Dusser et al., 1984; Rees et al., 1985; Marks et al., 1985; Langford et al., 1986; Utell et al., 1985). This clearance rate can be determined noninvasively in vivo by gamma camera imaging of the aerosolized ^{99m}Tc-DTPA deposited in the lung, representing generally first

order clearance kinetics since there is initially little build up of activity in the blood compartment due to rapid elimination of DTPA via the kidney. As indicated in Figure 12, DTPA retention halftimes will become much shorter when the reflection coefficient of the alveolar membrane decreases, i.e., when the lungs become more "leaky" due to damaged alveolar epithelium. Such damage has been demonstrated in acute and chronic lung injuries of different pathogenetic origins, including inflammatory reactions, edema, interstitial pulmonary diseases, pulmonary emboli, asthma, cigarette smoking, and ozone exposure (Chopra et al., 1979; Rinderknecht et al., 1980; Mason, 1985; Dolovich et al., 1982; Dusser et al., 1984; Mason et al., 1985; Buxton-Thomas et al., 1986; Kehrl et al., 1987).

Alveolar clearance of DTPA can also increase under physiological conditions when no lung injury is present, e.g., during exercise and at increased lung volumes (Meignan et al., 1986; O'Brodovich et al., 1986; Woolman et al., 1986). Thus, DTPA clearance does not only reflect the permeability of the alveolar membrane since those and other factors including sites of aerosol deposition and surface area can significantly influence DTPA clearance rates. Effros and Mason (1983) described the clearance kinetics of inhaled water soluble particles in analogy to CO diffusion studies by the relationship

$$C_t = C_o \cdot e^{-(PS/V)t} \qquad (4)$$

where

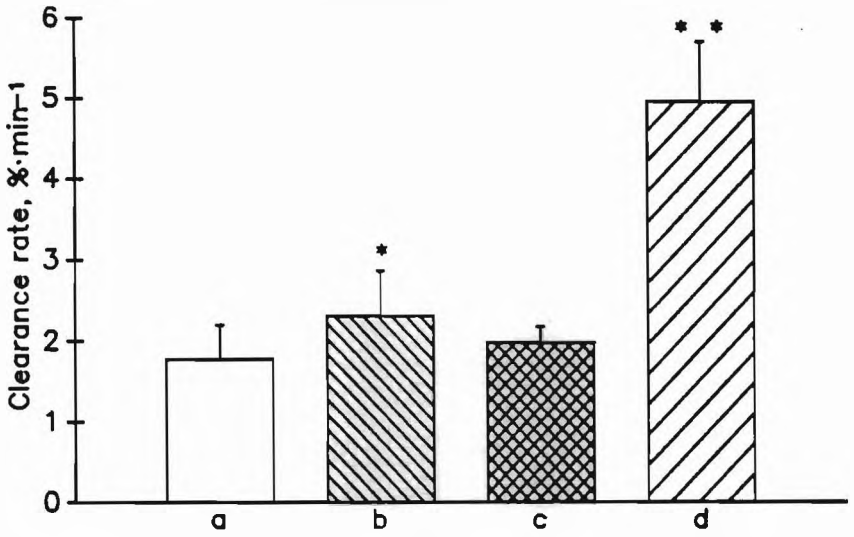
C_t = concentration in lung at time t (μg/g)
C_o = initial concentration in lung (μg/g)
P = permeability of the alveolar epithelium (cm/sec)
S = epithelial surface area (cm^2)
V = volume of solute distribution (cm^3; epithelial lining fluid volume)

If the ratio S/V remains constant, the changes in solute clearance reflect changes in permeability of the membrane only and clearance rates are relatively independent of changes in surface area (Effros and Mason, 1983). However, an increase in surface area will also increase solute clearance across the alveolar epithelium as seen in studies with increased lung volumes (Egan, 1982; Woolman et al., 1986; Rizk et al., 1984; Marks et al., 1985).

Figure 13 shows results of an experiment in our laboratory in which ^{99m}Tc-labeled aerosols were delivered for two minutes to anesthetized dogs at different lung volumes, and lung clearance of the solute was followed for 30 min thereafter at either spontaneous breathing or at increased lung volume (Oberdörster et al., 1985): When the solute aerosol was delivered at an increased lung volume (tidal volume 55 ml/kg body weight, b in Fig. 13) solute lung clearance was increased significantly over control levels (a in Fig. 13). Two minute ventilation at this same high lung volume prior to aerosol delivery at normal lung volume (tidal volume 13 ml/kg body weight, c in Fig. 13) did not change subsequent solute clearance. The most dramatic increase in lung solute clearance was seen when the solute aerosol was delivered at normal lung volume and clearance was measured under conditions of increased lung volume (d in Fig. 13). In this latter case, the ratio S/V in Eq. (4) increased since the alveolar surface area, but not the volume of distribution increased, and thus an increased surface area may partly explain the increased clearance rate. However, results from fluid instilled lungs suggest, that lung hyperinflation additionally increases the permeability of the membrane, P in Eq. (4), which could possibly be due to stretching of the interepithelial tight junctions (Effros and Mason, 1983).

Such junctional stretching during lung hyperinflation is also suggested from results of studies in rats with i.v. administered DTPA where the amount of DTPA diffusing into the alveolar space was found to be increased with increased lung volumes (Fiorica et al., 1988). In addition, high lung volumes might influence the diffusion characteristics of the solute - when delivered as aerosol - into the surface lining fluid, i.e., it may increase the diffusional spreading and thus increase the surface area available for transepithelial diffusion (O'Brodovich and Coates, 1987). Spreading on a flat surface occurs

FIGURE 13
Lung Volume and Solute Clearance



Alveolar clearance rates in dogs of ^{99m}Tc-DTPA administered for 2 min as an aerosol show the influence of lung volume (Oberdörster et al., 1986b). a: DTPA aerosol delivery at normal lung volume, clearance measurement at normal lung volume. b: DTPA aerosol delivery at high lung volume, clearance measurement at normal lung volume (significantly different from a, $p < 0.05$). c: Two minute ventilation at high lung volume prior to DTPA aerosol delivery at normal lung volume and clearance measurement at normal lung volume. d: DTPA aerosol delivery at normal lung volume and clearance measurement at high lung volume (significantly different from a, $p < 0.02$).

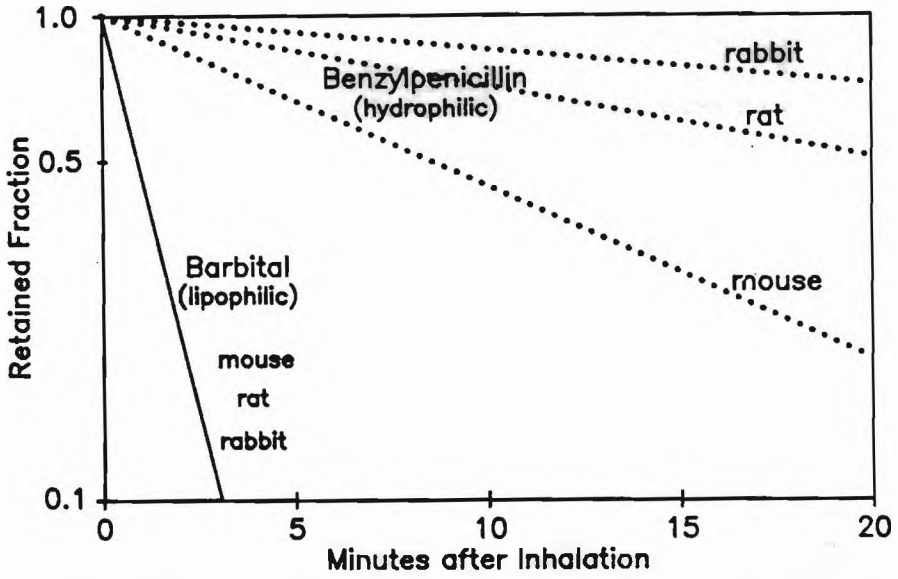
usually rapidly, within a few seconds, and thus should greatly exceed the lung clearance rate of the solute across the alveolar epithelium (Effros and Mason, 1983). However, the hydrophobic surface of the alveolar lining fluid could conceivably slow down the diffusion of hydrophilic solutes into the lining fluid (O'Brodovich and Coates, 1987), a factor that needs further investigation. It is interesting to speculate that delivery of the solute aerosol at high lung volumes in our study described above (b in Fig. 13) might have led to deposition of the particles in alveoli with less lining fluid (lower volume of distribution, V in Eq. (4) since they are not inflated during normal ventilation, thus explaining the observed faster lung clearance rate.

Although applying this technique of noninvasively measuring an index of alveolar permeability with ^{99m}Tc-DTPA aerosols clinically is very appealing, several unresolved questions require further basic research for interpreting results from this method before it should be used routinely. O'Brodovich and Coates (1987) also emphasized in a recent review that this method remains an experimental investigative tool that is not yet ready for widespread clinical application. For example, clarification is needed on questions related to the significance of lung surfactant; the stability of the ^{99m}Tc-DTPA complex (Nolop et al., 1986; Waldman et al., 1987; Dolovich et al., 1987); unexpected decreases in clearance rates in the beginning phases of an inflammatory reaction in the lung (Oberdörster et al., 1986a; Platner and Morrow, 1988); the importance of DTPA build-up in the blood compartment during accelerated lung clearance (Jones et al., 1982; Langford et al., 1986); the reproducibility within and between laboratories and standardization of the technique (O'Brodovich and Coates, 1987).

It is conceivable that the DTPA molecule is too small, representing a marker which is too sensitive towards small physiological changes in lung volume thus making it difficult to use it as a routine diagnostic tool for measuring an indicator of alveolar epithelial permeability. A solute tracer of larger molecular weight might be better suited for this purpose. The choice of such tracer depends on how its clearance is influenced by factors such as: site of deposition in respiratory tract; hydrophilicity, lipophilicity; chemical stability and reactions (binding, receptors); lung disorders and administered pharmaceuticals (see Jones, 1984 and Newhouse et al., 1987); recirculation (diffusion gradient, e.g., influenced by renal elimination); lung volume; physical exercise.

With regard to pulmonary solute clearance in different animal species it has been found that clearance of inhaled DTPA in dogs is faster than in humans, with pulmonary retention halftimes of about 30 minutes (Rizk et al., 1984; Oberdörster et al., 1986b). On the other hand, respective DTPA retention halftimes were longer in rabbits ($T_{1/2}$ = 127 min, Jefferies et al., 1984). A study in different species with a range of inhaled solutes showed that absorption of hydrophilic solutes was fastest in the mouse, followed by the rat and was slowest in the rabbit (Schanker et al., 1986). In contrast, a given inhaled lipophilic solute was absorbed at about the same rate in all three species (Fig. 14). Thus, lung clearance of hydrophilic solutes depends on both the animal species and the solute molecular weight whereas for lipophilic solutes it seems to depend only on their lipid/water partition coefficients and to be independent of animal species. Since the ratio of clearance rates between species was found to be constant for hydrophilic solutes, reflecting

FIGURE 14
Lung Clearance of Inhaled Solutes in Different Species



Species dependency was observed for hydrophilic, but not for lipophilic solutes. Ratios of clearance rates of different hydrophilic compounds for mouse:rat:rabbit were remarkably constant with approximately 0.4:1:2.5. Respective clearance rates for different hydrophilic compounds increase with the molecular size of the compound. In contrast, clearance rates for lipophilic compounds increases with their lipid/water partition coefficient (after Schanker et al., 1986).

the species specific porosity of the epithelium, it may be possible to predict the rate of pulmonary absorption of a given drug in one species from data obtained for the same drug in another species (Schanker et al., 1986).

A leaky alveolar epithelium in diseased lungs leading to increases of the clearance of hydrophilic solutes from the alveolar space implies that lung retention of soluble compounds given as aerosols is decreased compared to a healthy lung, e.g., a therapeutical aerosol could have a significantly shorter residence time - and thus is less effective - at a target site in the lung than would be expected from its kinetics under healthy conditions. Encapsulation of such therapeutic agents in particles with membranes of low in vivo solubility could increase their pulmonary retention. Obviously, such modifications depend also on whether a systemic distribution of an inhaled therapeutic agent or a more localized effect in the lung is desired (Lourenco and Cotromanes, 1982).

Chemical reactions influencing pulmonary retention of solutes (Fig. 1, Table 2) are of particular importance for inhalation toxicology. Many water soluble inhaled substances will not be cleared from the alveolar space simply by diffusional processes but may react with lung fluids or cells, e.g., being hydrolyzed to less soluble compounds or bound to proteins. Resulting clearance rates are unpredictable and can also differ quite significantly among animal species. Conversely, substances with low water solubility can be cleared from the lungs quite rapidly because their in vivo dissolution in the lung is very rapid. As mentioned in the Introduction, examples both for a fast lung clearance of water insoluble compounds (high in vivo solubility) and of low lung clearance of water soluble compounds (chemical binding) are found after inhalation of heavy metals. For instance, inhaled aerosols of ZnO and Pb $(OH)_2$ (low water solubility) and other lead compounds were found to have a monoexponential retention halftime of a few hours only (Bianco et al., 1974; Oberdörster et al., 1979; Morrow et al., 1980). Inhaled aerosols of $CdCl_2$ (water soluble), on the other hand, showed a much longer pulmonary retention than predicted from their water solubility and molecular size. Moreover, pulmonary retention of $CdCl_2$ after a single exposure is significantly different between rats, dogs, and monkeys (Fig. 15, Oberdörster and Cox, 1988): rats exhibited a monoexponential clearance pattern corresponding to a halftime of 85 days, in dogs 70% of the deposited $CdCl_2$ was cleared with a retention halftime of 153 days and in monkeys a monoexponential clearance with a retention halftime of 818 days was found over an observation period of 650 days.

Although this species dependent pulmonary clearance of water soluble Cd-compounds appears to be very similar to the pulmonary clearance characteristics of highly insoluble particles (Fig. 5) - which is related to AM function - pulmonary clearance of cadmium is not mediated by AM. This was demonstrated in rats when during long-term inhalation of CdO aerosols the alveolar clearance of Fe_2O_3 test particles was significantly retarded, but not that of a $CdCl_2$ test aerosol (Oberdörster and Hochrainer, 1980). Water insoluble CdO particles are cleared with the same rates as $CdCl_2$, due to a rapid initial in vivo dissolution of those particles, probably in the phagolysosomes of AM (Hadley et al., 1980; Lundborg et al., 1984). Following this rapid in vivo dissolution of CdO, subsequent elimination occurs at the slow clearance rate of soluble cadmium compounds. This slow clearance may involve binding to serum and cellular proteins, most likely including metallothionein (Oberdörster, 1986) which is induced in the lung due to cadmium exposure (Post et al., 1982).

The measured pulmonary retention halftimes of soluble particles are undoubtedly the result of several clearance processes whose relative contributions change depending on the physico-chemical properties of a specific particulate matter. These processes - whether reactions with specific ligands, diffusion rates across membranes, dissolution rates in AM, or mechanical transport rates - are of different magnitude in different mammalian species and thus make it difficult or even impossible to extrapolate directly results of pulmonary retention measurements of a specific compound in animals to humans.

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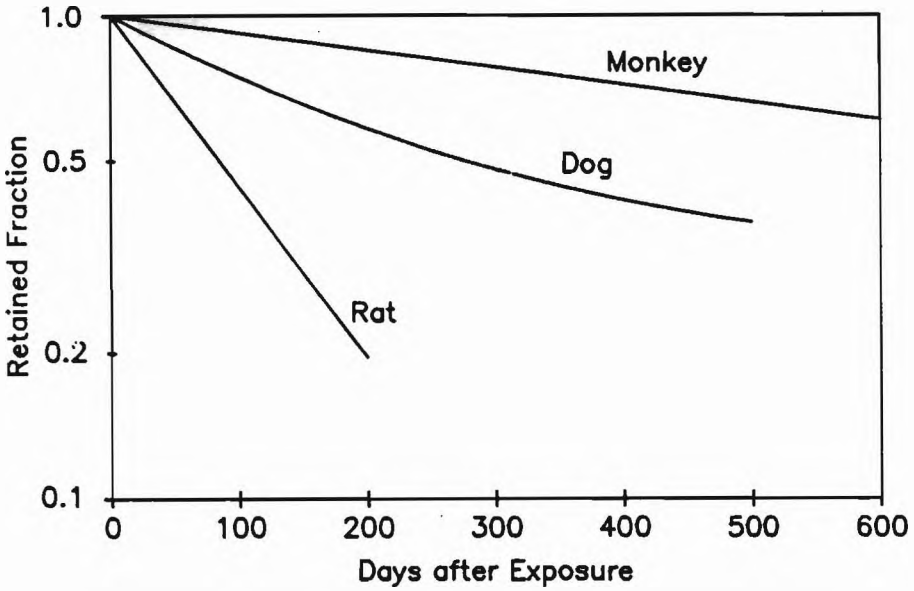
FIGURE 15
Pulmonary Retention of Inhaled Water Soluble $CdCl_2$
Particles in Different Species (Oberdörster and Cox, 1988)



Retention measurements were started one day after exposure to $CdCl_2$ aerosol. Pulmonary cadmium retention in rat and monkey could be described by a monoexponential term with biological retention halftimes of 85 days and 835 days, respectively; in dogs, a biological retention halftime of 153 days plus a constant fitted the data best.

CONCLUDING REMARKS

Basic differences exist in the clearance of insoluble and soluble inhaled particles from the respiratory tract. Conducting airway clearance of insoluble particles is fast and maybe essentially complete within one day, although results of recent studies indicate that retention in the conducting airways may be substantially longer than generally presumed. Possibly, airway macrophages which phagocytice particles in this region may act as "inhibitors" of an otherwise fast bronchial clearance of insoluble particles. Inhaled soluble particles are cleared from both the conducting and the alveolar zone at a very rapid rate with corresponding retention halftimes of minutes or hours, depending on lipophilicity, hydrophilicity, and molecular size. However, binding with and to tissue and cellular components and adsorption onto highly insoluble particles can increase retention halftimes significantly to days and months. In vivo retention of an inhaled hydrophilic solute is longer in the conducting airways than in the alveolar region (Brown and Schanker, 1983; Oberdörster et al., 1986b), although pore equivalents seem to be of larger size in bronchial than alveolar epithelium (Gatzy and Boucher, 1982). This longer retention seen in vivo is possibly due to differences in the thickness and composition of the liquid layer lining the epithelial surfaces of alveoli and conducting airways.

Alveolar clearance mechanisms for solute particles involve mainly diffusion and transport via intercellular and transcellular pathways, whereas insoluble particles are transported up the mucociliary escalator mostly after phagocytosis by alveolar macrophages, and a minor fraction may leave the lung via this pathway as free particles. Effective pulmonary clearance rates of inhaled particulate compounds are determined by their mechanical clearance rate, their dissolution rate and the clearance rate of the dissolved compound. The latter can involve diffusion, active transport or chemical reactions in the lung which

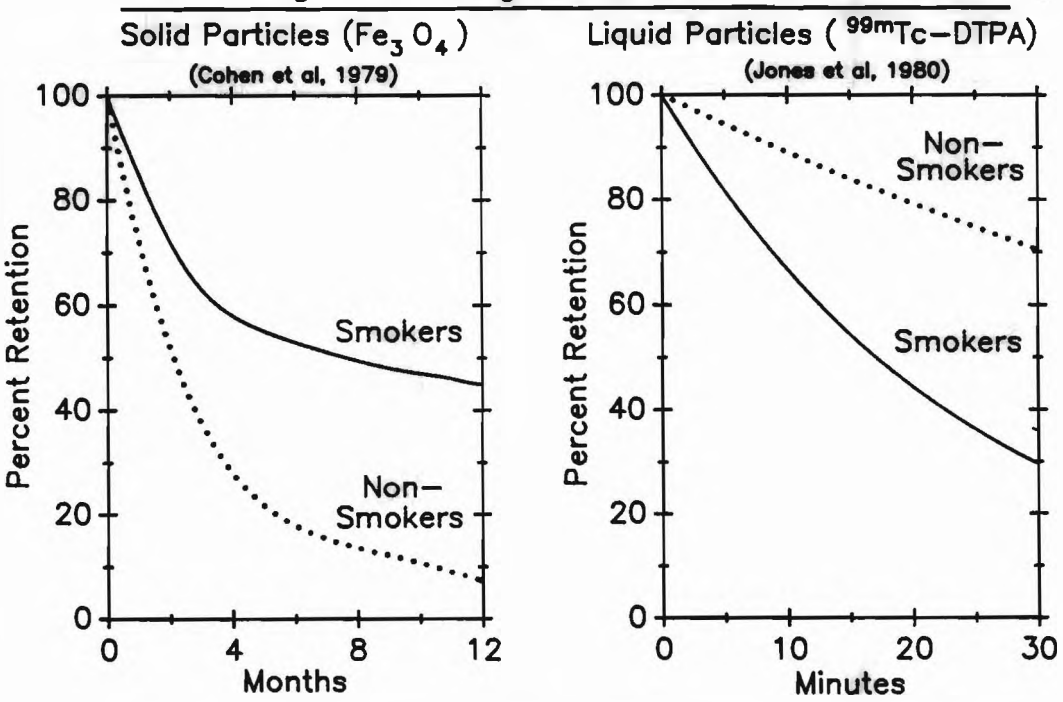
- like the other factors - can be different in different animal species. It is therefore difficult to determine or to predict mechanical clearance rates of particles with unknown in vivo solubility and reactivity from in vivo retention measurements in a given animal species. Estimated mechanical pulmonary clearance rates of solid particles showed a species dependency and became slower with time. However, some uncertainties remain with regard to the accuracy of the estimates of in vivo dissolution rates and transport rates of particles into lymph nodes which need to be known for calculating mechanical clearance rates.

Although the mechanical clearance rate of insoluble particles is very slow for the alveolar compartment compared to the tracheobronchial region, it is still very efficient in handling particulate burdens resulting from inhalation of typical dust concentrations in ambient air. However, studies in rodents showed that under extremely dusty conditions lasting for an extended period of time AM mediated clearance becomes increasingly impaired resulting in the development of chronic lung disease. Transepithelial transport of solid particles across the alveolar epithelium occurs normally at a low rate only, but can increase substantially under conditions of high particulate lung burdens. It appears that whenever AM-mediated particle clearance is impaired, an increased penetration of particles into the interstitium takes place and an increased build-up of particulate burden in the regional lymph nodes occurs (e.g., Ferin and Feldstein, 1978).

Conceivably, AM function may be affected synergistically by a combination of high exposure concentrations and cytotoxicity of the inhaled compounds, e.g., inhalation of high concentrations of quartz and asbestos (Ferin, 1972; Ferin and Leach, 1976) or of diesel exhaust with its many chemicals of known and unknown toxicity in both the gas and particulate phase (Chan et al., 1984; Wolff et al., 1987). Under such conditions, AM clearance function should be affected at lower particulate lung burdens than at those with "nuisance" particles of low toxicity like TiO_2. The results of Wolff et al. (1987) seem to support this view since exposure of rats for 18 months to low concentrations of diesel exhaust resulting in a lung burden of 320 µg soot/lung - below a concentration of particles of low toxicity in the lung known to cause impaired lung clearance in rats - led to an accelerated accumulation of soot upon further exposure.

Diseases of the lung can affect clearance of soluble and insoluble particles differently: elimination of inhaled insoluble particles is retarded, whereas elimination of inhaled solute particles is accelerated. This is demonstrated in Figure 16 in which the effect of smoking on alveolar lung clearance of highly insoluble and highly soluble particles is shown. Long-term lung clearance of trace amounts of magnetite test particles was significantly decreased in smokers (Cohen et al., 1979), whereas ^{99m}Tc-DTPA solute lung clearance in smokers was significantly increased (Jones et al., 1980). In addition to showing the qualitative differences in the effect of smoking on alveolar lung clearance, differences in the rate of clearance between the two particle types become apparent from the time scale, months for the solid particles and minutes for the liquid particles (Fig. 16). Obviously, such differences are readily explained by the different underlying clearance mechanisms for these two types of inhaled particles. However, in both cases AM probably play a central role in the mechanisms of altered alveolar clearance in lungs of smokers and nonsmokers: Solid particle clearance decreased in smokers due to impaired AM function (Green, 1985), and solute clearance may have increased due to effects on the alveolar epithelial barrier of mediators released from activated AM (Jones et al., 1983). As already mentioned, the implications for diseased lungs - in this case, smokers' lungs - are that retention of water soluble therapeutic aerosols in the deep lung may be less than anticipated and that - in contrast - smokers accumulate significantly more of deposited nuisance dust or other solid particles in the alveolar region than nonsmokers. The latter was corroborated by findings of an increased retention of particulate material in the lungs of smokers (Churg and Wiggs, 1987). However, it is possible that this greater retention and resulting dust accumulation in lungs of smokers could somewhat be offset by a lower pulmonary deposition due to a greater central deposition in their conducting airways if chronic bronchitis is present.

FIGURE 16
Smoking and Lung Clearance



In lung injury caused by smoking, pulmonary clearance of highly insoluble test particles (Fe_3O_4) is retarded probably due to decreased AM function (Green, 1985); predictably, smokers will accumulate in addition to smoke particles more of other inhaled particles in their lungs than nonsmokers. Retention of Fe_3O_4 test particles was measured noninvasively by magnetopneumography in nine nonsmoking and three heavy smoking male subjects, and the authors concluded that smoking was the cause of retardation of test particle clearance (Cohen et al., 1979). Bohning et al. (1982) came to the same conclusion in a similar study after inhalation of radiolabeled polystyrene test particles by smokers and nonsmokers. In contrast, pulmonary clearance of the hydrophilic solute DTPA inhaled as an aerosol is increased in smokers due to a more leaky alveolar epithelium. The DTPA study (Jones et al., 1980) was the first study of this kind measuring lung clearance of ^{99m}Tc-DTPA with a gamma camera in smokers and nonsmokers. Mean retention halftimes were 59 min for nonsmokers and 20 min for smokers. The result of this study in ten smokers and ten nonsmokers was confirmed later in other studies (Dolovich et al., 1982; Mason et al., 1983; Mason, 1985).

Knowledge of lung clearance processes of inhaled particles in the healthy lung is essential for the understanding of effects of inhaled environmental, occupational and clinical aerosols. It is also a necessary presupposition for dosimetric extrapolation modeling of results from animal inhalation studies to humans since retained doses of substances at pulmonary target sites are largely determined by their clearance behavior. Unraveling of cellular and molecular bases of lung clearance mechanisms requires considerable additional work. In particular, the mechanisms of clearance behavior in lung diseases are an important issue which needs further attention.

ACKNOWLEDGEMENTS

The author gratefully acknowledges the helpful review and valuable suggestions by Dr. P.E. Morrow, Dr. J. Ferin, Dr. M.J. Utell, and Dr. S.C. Soderholm. Special thanks goes to P.A. Morse and N.L. Corson for helping to prepare the figures of this article. Partial support by NIEHS grants ES 01247 and ES 01248 is acknowledged.

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Article received: March 8, 1988
Reviewed by: W.M. Foster

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