QUANTITATIVE ANALYSIS OF PARTICLE TRANSLOCATION WITHIN THE LUNG.

J. Ferin, S. Soderholm, and G. Oberdörster University of Rochester, Environmental Health Sciences Center, Roch., NY 14642, USA

We have shown that ultrafine particles (diameter ~20 nm) elicit an acute inflammatory response, among others, after being deposited in the alveoli. The inflammatory response seems to be a sequelae of the interstitialization process which is substantially increased in the case of the ultrafine particles compared to particles of larger size(1). The translocation of deposited particles from the alveoli into the pulmonary tissue *per se* is of interest in particle-lung interaction studies. We have now developed two approaches for quantitative determination of particles in various rat lung compartments during and as a result of translocation. One is based on an extensive lavage of the excised lung, followed by chemical analysis of particle content in the lavaged lung and extra-pulmonary lymph nodes, and of the lavaged cells and fluid. The latter is assumed to be indicative of particles localized in the alveoli, the former of translocated particles. The second approach is based on magnetometry. Using an array of eight flux-gate magnetometers the particle lung burden of magnetite particles is analyzed *in vivo*. This noninvasive measurement is independent of the location of the magnetic material within the lung, a significant improvement over previous magnetometric systems. After magnetization of the particles by an external magnetic field, the magnetic signal and its relaxation over 15 min. are recorded. This measurement makes it possible to assess the particle lung burden over long periods of time. The use of signal relaxation has the potential to distinguish between intra- and extracellular material *in vivo*. The present interpretation of the results indicate that after instillation or inhalation of ~1 mg of magnetite, the clearance half-time of "relaxing" material is 40-80 days, as expected from other studies. These results seem to be consistent with approaches using chemistry for quantitative analysis. The magnetometric method is less sensitive than chemical analysis and is limited to particles with magnetic properties like magnetite, but it has the potential for repeated noninvasive measurements of distinct particle populations in the same animal.

Acknowledgement: This project was supported in part by grants OH02772-02 from NIOSH of the CDC and ES04872 from NIEHS.

(1) Ferin, J., Oberdörster, G., Soderholm, S.C. and Gelein, R. (1991). Pulmonary tissue access of ultrafine particles. *J. Aerosol Med.* 4(1): 57-68.

PULMONARY CLEARANCE OF INHALED PARTICLES 24 TO 48 HOURS POST DEPOSITION: EFFECT OF BETA-ADRENERGIC STIMULATION.

W.D.Bennett, W.F. Chapman, J.C. Lay, and T.R. Gerrity. Center for Environmental Medicine, UNC at Chapel Hill and Clinical Research Branch, US Environmental Protection Agency, Chapel Hill, NC 27599.

Recent studies have suggested considerable particle retention in the bronchial, ciliated airways 24 hours after depositing in the lung. Inhalation of beta-adrenergic agonists have been shown to enhance clearance of inhaled particles from these airways. A significant presence of particles in the ciliated airways at 24 hours post deposition may be indicated if beta-adrenergic treatment between 24 and 48 hours is shown to enhance particle clearance during this same period. We tested this hypothesis in ten young, normal subjects who inhaled Tc99m-iron oxide particles (5μm MMAD) on three separate occasions. Following the first aerosol exposure, each subject inhaled a dose of albuterol sufficient to decrease specific airway resistance by 63% (mean baseline sRaw = 3.47 +/-0.99 cm H_2O-sec, and post albuterol sRaw = 1.27 +/- 0.28 cm H_2O-sec) and clearance was measured by gamma camera over a 3 hour period. For the subsequent two aerosol exposures, baseline mucociliary clearance was measured, again over the initial 3 hour period, and then retention of particles was monitored with a six crystal gamma detector between 24 and 48 hours. During this 24-48 hour period, each subject inhaled 2 doses of either albuterol (A) (a similar dose to that described above) or saline (S) (double-blinded design). We found that albuterol significantly enhanced clearance at one hour post deposition. Mean retention (as a fraction of initial deposition) at 1 hour (R_1) with albuterol was R_1 = .39 +/- 0.11 vs. control(A) R_1 =.76 +/- 0.11 and control(S) R_1 = .74 +/- 0.12, $p < .001$ by repeated measures analysis. On the other hand, albuterol did not significantly enhance clearance of particles between 24 and 48 hours, e.g. as a fraction of 24 hour retention mean saline R_{31} =.84 +/- .05(SD) and mean albuterol R_{31} =.81 +/- .04, and similarly mean saline R_{48} =.68 +/- .15 and mean albuterol R_{48} =.65 +/- .12. These data do not support the hypothesis that a significant number of particles are present on the ciliated airways at 24 hours post deposition. There may be particles retained in the airways at this time but not accessible to clearance by the mucociliary system. Supported by USEPA Cooperative Agreement CR812738 and NHBLI FIRST Award HL39411. This is an abstract of a proposed presentation and does not necessarily reflect EPA policy.

A SIMULTANEOUS DUAL TRACER METHOD OF MEASURING BRONCHIAL WALL PERMEABILITY IN NON-SMOKING NORMAL SUBJECTS AND ASTHMATICS.

D.C.Currie, B.D.Jones, T.R.Leigh, P.A.Andrews, R.F.Jewkes, J.V.Collins, T.W.Evans. Westminster Hospital, Horseferry Rd, London, SW1P 2AP, UK.

Bronchial inflammation, a cardinal feature of asthma, is believed to be reflected by an increase in bronchial wall permeability. Inhaled nebulized Tc^{99m} DTPA is cleared from the airway by two mechanisms: via the bronchial wall into the blood (permeability), and via the tracheal lumen by mucociliary clearance and cough. Bronchial wall permeability has previously been quantified by subtracting the clearance rate of Tc^{99m} human serum albumin (HSA), a non-permeable tracer cleared by mucociliary clearance and cough, from the total clearance rate for DTPA (Bennett WD et al, Am Rev Resp Dis 1989;139:1132-38). However, clearance measurements for the two substances were made on different days, ignoring the possibility of variations in mucociliary clearance rates and cough. We have modified the technique, in order to overcome this problem, by measuring simultaneously the clearance rates of both DTPA and HSA from large airways using In^{113m} and Tc^{99m} as the respective labels. In order to promote central deposition of the radiolabelled substances we used a DeVilbiss Ultraneb 99 ultrasonic nebuliser producing particles of median mass diameter 5.5μm with normal tidal breathing. Simultaneous clearances of In^{113m}-DTPA and Tc^{99m}-HSA were measured over a 60 minute period using a gamma camera with a medium energy (400keV) collimator. Five non-smoking normal subjects (mean age 35 yrs, range 32-39 yrs), and five asthmatic subjects (mean age 47 yrs, range 29-63 yrs, mean FEV_1 = 72% predicted, range 51%-103%) receiving regular inhaled corticosteroids, were studied on three and one occasions respectively. Permeability $t_{1/2}$, expressed as the calculated time for half the DTPA to be cleared through the bronchial wall, for the normal subjects gave a mean value of 187 minutes (range 110-316 minutes). Permeability rates on the 3 occasions for each normal subject showed little variation (minimum value/maximum value x 100 ranged from 62%-88%). In the asthmatic group, permeability $t_{1/2}$ ranged from 82 minutes to >1000 minutes (mean 660 minutes). Central deposition of the tracer was confirmed by gamma camera imaging. The technique was well-tolerated in all subjects, simple to reproduce, and gave significant advantages over single nuclide techniques. It will now be critically evaluated in a variety of bronchial disorders.

A COMPUTATIONAL MODEL OF PARTICLE DEPOSITION IN ALVEOLI AND ALVEOLAR DUCTS.

S. Anjilvel, R.R. Mercer and J.D. Crapo. Duke University Medical Center, Durham, NC, USA.

Current models of particle dosimetry in the deep lung have been based on analytic calculations of deposition fractions due to diffusion, sedimentation, and impaction. Such models assume a simple geometry with steady, parabolic air flow profiles, and assume independence of the deposition mechanisms. We introduce a Monte Carlo simulation model of particle transport and deposition in alveolated ducts. It uses realistic geometry, calculates unsteady flow patterns, and predicts deposition by directly modeling the fundamental transport processes. We have developed anatomically correct, three-dimensional models of the pulmonary acinus for rats and humans. These structural models were used to construct a two-dimensional model of acinar air flow. The acinus is represented by a planar region whose boundary moves in a specified manner that simulates breathing. We numerically solve the Navier-Stokes equations that govern fluid flow to obtain the air velocity profiles in the region. The velocity field is then used to simulate the motion of a single particle introduced at the entrance to the alveolar duct network. The time interval of interest is divided into a number of small steps. The position of the particle at each step is computed using the position at the previous step and by calculating the forces acting on the particle between steps. These forces are gravity, viscous drag, and diffusion. Diffusion is simulated by adding a random component to the particle motion during a time step. The particle is tracked until it exits the region or is deposited on the lung surface. This procedure is repeated until the number of particles studied is large enough to permit statistical inference of the deposition fraction and pattern. We found that deposition at the first alveolar duct bifurcation distal to the terminal bronchiole, a point of focal injury due to inhaled particles, was twice that of nearby alveolar septa. We also found that the presence of alveoli enhances the total deposition within a duct because particles tend to intercept alveolar septal edges.

AMERICAN REVIEW OF
Respiratory Disease

SUPPLEMENT

April 1992 Volume 145 Number 4, Part 2

AMERICAN LUNG ASSOCIATION • AMERICAN THORACIC SOCIETY

ABSTRACTS

1992 International Conference

May 17–20, 1992 • Miami Beach, Florida

This special supplement of the *American Review of Respiratory Disease* contains abstracts of the scientific papers to be presented at the 1992 International Conference, which is sponsored by the American Lung Association and the American Thoracic Society. The abstracts appear in order of presentation, from Sunday, May 17 through Wednesday, May 20 and are identified by session code numbers. To assist in planning a personal schedule at the Conference, the time and place of each presentation is also provided.