of similar growth mediators. Proinflammatory cytokine gene expression was also assessed by *in situ* hybridization on paraffin sections. Statistically significant increases in pulmonary surfactant were observed only in the highest dose group. This was present during exposure and persisted through 6 mos. post-exposure. Expression of MIP-1 mRNA was found associated in cells in the alveolar spaces. MIP expression was seen in the high dose group where it persisted for up to 1 yr. Initially, expression of MIP was observed independent of cellular particle content, while at longer times only particle laden cells were positive. Growth factor production *in vitro* showed minor alterations at all doses but persistent effects only at the highest dose. These results suggest a pattern of persistent responses after inhalation exposure at high lung burdens and is consistent with a threshold for adverse effects.

515 PULMONARY RESPONSES TO AMIODARONE IN HAMSTERS: COMPARISON OF INTRATRACHEAL AND ORAL ADMINISTRATIONS

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Amiodarone (AD) produces a transient pulmonary fibrosis in hamsters after intratracheal (i.t.) instillation. The goal of this study was to explore the mechanism of AD-induced pulmonary fibrosis in the hamster model. Bronchoalveolar lavage (BAL) parameters during the development of fibrosis following i.t. AD in hamsters were examined; the responses to oral AD in hamsters were examined for comparison to responses to i.t. AD in an effort to explore the roles of inflammation, phospholipidosis, and lung drug burden in AD-induced pulmonary disease. Two i.t. instillations of AD on days 0 and 7 in hamsters produced variable increases in lavage macrophage, neutrophil, and eosinophil number through day 28. I.T. AD also increased the permeability of the alveolar-capillary barrier as evidenced by an increase in BAL fluid albumin on day 8. Pulmonary phospholipidosis was not induced by i.t. AD and only small amounts of AD and its metabolite desethylAD (dAD) were detected in lung tissue through day 10 after instillations on days 0 and 7. The repeated oral administration of AD did not result in pulmonary fibrosis during the 35 day course of this study. Oral AD did cause a sustained increase in BAL fluid neutrophil number; other BAL cells were only slightly affected. Oral AD did not increase BAL fluid albumin content but a prominent BAL cell phospholipidosis was noted. Measurement of AD and dAD in lung tissue demonstrated a substantial sequestration of drug and metabolite after oral treatment with AD. The results of this study indicate that lung drug burden, pulmonary phospholipidosis, and lung neutrophil influx are not crucial factors in the development of AD-induced pulmonary fibrosis in hamsters. This study supports the involvement of physical damage to the lung and/or pulmonary eosinophilia in the generation of AD-induced pulmonary fibrosis in hamsters. (NIH/NIGMS Training Grant T3GM07039).

516 PARTIAL PROTECTION FROM ACUTE SILICA TOXICITY BY DEXAMETHASONE IN RATS

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The generation of silica dust and human exposure to this dust is of great occupational concern because it causes pulmonary inflammation/damage that ultimately proceeds to fibrosis. The initial phase of the toxic response occurs within 2 hours of exposure although the "classical" sign of inflammation (neutrophil influx) is absent. The purpose of this study was to differentiate between the toxicities due to the intrinsic properties of silica, and those due the cellular infiltration. Male Fischer 344 rats were intratracheally (i.t.) instilled with silica (10 mg/100 g bw) or saline vehicle. Two hours post-instillation, half of each group received either steroid (dexamethasone 8 mg/kg, i.p.), in an attempt to suppress cellular infiltration and function, or saline vehicle. Post-treatment continued on alternate days. Animals were killed on day 2 or 8 prior to that day's scheduled injection. Cellular (total and differential cell counts) and biochemical (β-glucuronidase [β-glu] and albumin) parameters of inflammation/damage were evaluated in the broncho-alveolar lavage (BAL). At 2 days, silica caused a neutrophilia that was reversed by continued steroid injections up to day 8. BAL albumin and β-glu were significantly elevated in response to silica at both times despite the presence of steroid. These data suggest the intrinsic properties of silica play a primary role in the toxicities following i.t. instillation. However, the transient cellular influx at day 2 may initiate the inflammatory cascade. To eliminate the early influx of cells, a steroid pre-treatment was employed in addition to the post-treatment. Rats received i.p. steroid or saline on days -5, -3, and -1. On day 0, rats from each group received i.t. silica or saline. Two hours after the instillations and on alternate days after, rats received i.p. steroid or saline identical to pre-treatment. On days 2 and 8 the cellular response to silica was suppressed by steroid, but β-glu activity was significantly elevated. Although elevated over control levels, BAL albumin content of the steroid/silica group, at days 2 and 8, was markedly suppressed when compared to values from the steroid post-treatment protocol. The addition of the steroid pre-treatment seems to afford a greater protective effect than does the post-treatment alone, implicating the cells as well as the silica itself contribute to the toxic response. (Supported by NIOSH Grant U60/CCU306149-03).

517 *IN VIVO* PNEUMOTOXICITY OF RESPIRABLE WELDING FUME PARTICLES IN A RAT BIOASSAY MODEL

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Using an *in vivo* rat bioassay model, we compared the potential of three welding fume samples generated during electric arc welding to elicit lung inflammation or injury. Particles were collected from conventional spray (mild steel or stainless steel electrode wire) or pulsed current (mild steel electrode wire) welding. The samples were sized by laser scanning confocal microscopy and were measured to be of respirable size with mean diameters $<2\ \mu$. CD/VAF rats were dosed intratracheally with the three welding fume samples, and with a relatively inert dust (iron oxide), a pneumotoxic, inflammatory dust (silica), and a vehicle control (saline) at doses of 0.2, 1.0, and 5.0 mg/100 g b wt. Bronchoalveolar lavage (BAL) was performed 1, 7, and 14 days post-instillation, and indicators of pulmonary damage (neutrophils, albumin, lactate dehydrogenase and β-n-acetyl glucosaminidase activities) were assessed in the BAL fluid. For all three doses, no consistent differences were observed in the pulmonary response of the three welding fume samples 1 day post-exposure. However, by 14 days, animals instilled with stainless steel (1.0 mg/100 g b wt) had significant elevations ($p < 0.05$) in lung damage when compared with the two treatment groups exposed to mild steel welding fume. Over the observation period, the results observed in the stainless steel group closely followed the elevated response ($p < 0.05$) seen with the silica group, and by 14 days, there were no differences in any of the parameters measured among the vehicle control, two mild steel, and iron oxide groups. We have demonstrated that welding fume particles generated from wires of different composition produce different pulmonary responses. However, in comparing particles generated from the mild steel wire using different power supplies, no differences were observed. (Supported by NIOSH grant #U60/CCU109979-01).

518 STRUCTURAL INTEGRITY OF TRACHEAL EPITHELIAL CELLS IN SEPTIC SHOCK AND ARDS CAN BE MAINTAINED BY BLOCKADE OF THE INTERLEUKIN-1 RECEPTOR

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We have previously shown *in vivo* morphological damage to tracheal epithelial cells by endotoxin (ENDT). Comparison of trachea from anesthetized male Sprague-Dawley rats receiving only *Escherichia coli* ENDT (6 mg/kg) was made with those receiving interleukin-1 receptor antagonist (IL-1ra) (0.2 mg/kg/min IV) beginning one hour prior to ENDT. When the mean arterial pressure (MAP) dropped to 40 mmHg (4 to 6 hrs.) in those animals receiving only ENDT, the tissues were taken and processed for electron microscopy (EM). Since MAP did not drop significantly in those animals receiving IL-1 ra + ENDT tissues were taken 6 hrs after ENDT and processed for EM. Extensive damage of tracheal epithelial cells was noted with ENDT alone but no damage was noted in animals receiving IL-1 ra. Subsequent *in vitro* studies of tracheal (3×6 mm strips) tissue was incubated *in vitro* in Dulbecco's Modified Eagle Medium with and without IL-1ra (1 mg/ml) over a 5 hr period for the following groups: 1) tracheal tissue alone, 2) tracheal tissue plus ENDT (1–250 μg/ml), 3) tracheal tissue with (neutrophils) PMN (separated by centrifugation and Ficoll layering from blood of the same rat), and 4) tracheal tissue plus PMN plus ENDT. The tissue was then processed for electron microscopy. The *in vitro* assessment showed no damage to epithelial cells in groups with and without IL-1ra in tracheal tissue alone, tracheal tissue plus ENDT, or tracheal tissue incubated with PMN. Tracheal tissue plus PMN plus ENDT showed epithelial cell damage without IL-1ra and not with IL-1ra. Thus the *in vitro* model as well as the *in vivo* model demonstrates IL-1ra affords protection in this rat model of sepsis and ARDS.

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