the p50 subunit (p50-cys^{62}) with the DNA κB binding site. We evaluated the effects of mercuric ion (Hg^{2+}), a potent thiol binding agent, on the expression of NF-κB in normal kidney epithelial (NRK) cells. The DNA binding of NF-κB in nuclear extracts was determined by gel shift assays using a ^{32}P-labeled oligonucleotide containing the κB consensus sequence. Both constitutive and LPS-inducible forms of NF-κB were readily detected in NRK cells. The expression of the inducible form of NF-κB was prevented in a dose-related manner by Hg^{2+} (100–250 μm) added to DNA binding reactions. Given the presence of ~250 μM DDT in the binding reaction, the concentration of free Hg^{2+} which elicited full inhibition of NF-κB binding was estimated to be as low as 25 μM. The Hg^{2+} block of NF-κB-DNA binding was prevented in a dose-related manner by competitive thiols, DTT and β-ME, in the range 0.5–2 mM. In contrast, the non-thiol antioxidants, BHA and vitamin E, were unable to reverse the effects of Hg^{2+} at comparable concentrations in the binding reaction. These results indicate that Hg^{2+}, at very low levels, prevents NF-κB expression most likely by blocking the interaction of the NF-κB binding domain (p50-cys^{62}) with the DNA κB binding site. Prevention of NF-κB expression may underlie apoptotic or other cytotoxic responses associated with low level Hg^{2+} exposure in kidney epithelial cells. Supported by ES04696 and Center Grant P30 ES07033.

1860 RENAL PROTEIN BIOMARKERS OF LEAD EXPOSURE.

M H Kanitz[1], H Zhu[1], J E Snawder[1], W J Moorman[1], S R Skaggs[1], C D Fultz[2], F A Witzmann[2], and R E Savage[1]. [1]*Experimental Toxicology Branch DBBS, NIOSH, Cincinnati, OH;* [2]*Molec. Anat Lab, Indiana Univ. Purdue Univ., Columbus, IN.*

To develop a set of protein markers of renal lead exposure and effect, we investigated renal protein expression while approximating occupational lead exposure at subchronic, low blood levels. Lead was administered to male Dutch Belted rabbits as a lead acetate solution adjusted weekly to achieve and maintain the target blood lead levels of 0, 20, 40, and 80 μg/dL for 15 weeks. Rabbits were sacrificed and kidneys removed and frozen. The homogenates were solubilized for large-scale two-dimensional electrophoresis (2-DE). Proteins were separated by conventional ISO-DALT 2-DE, gels were stained, and the resulting protein patterns image-analyzed. Minor proteins were quantitatively altered ($P<.05$) by lead exposure (12 proteins by 20μg/dL exposure, 25 by 40μg/dL and 102 by 80μg/dL). The more liberal confidence interval may be associated with a high probability of Type I error. Using the more reliable interval $P<.001$, 40μg/L blood lead resulted in only one protein alteration and 80μg/dL affected 14 proteins. Although the identity of all effected proteins remains unknown, we have tentatively identified a set of quantitatively altered charge variants as isoforms of glutathione S-transferase (GST) based on similar observations in rodents subjected to short-term, very high lead exposures. The significance of the protein alterations as markers of toxicity and toxic mechanism awaits their conclusive identification. These experiments are currently underway. Supported by NIOSH and AFOSR # F49620-96-1-0156.

1861 REGIONAL PROTEIN ALTERATIONS IN RAT KIDNEYS INDUCED BY LEAD EXPOSURE.

F A Witzmann[1], D A Daggett[2], C D Fultz[1], S E Kornguth[2], L S Wright[2], and F L Siegel[2]. [1]*Molecular Anatomy Lab, Indiana Univ. Purdue Univ., Columbus IN.* [2]*Waisman Center, University of Wisconsin, Madison WI.*

Lead is a hazardous substance in humans and a renal carcinogen in adult rodents. Previous studies have detected lead-induced increases in specific isoforms of glutathione S-transferase in distinct kidney cell types preceding irreversible renal damage. Other urinary markers have been observed after the onset of lead-induced renal injury, as well. Histologic examination suggests that lead-induced damage is confined primarily to the proximal tubular epithelium, located in the renal cortex. The present study was undertaken to explore whether protein markers of lead exposure and toxicity, besides GST, might be detected in kidney cortical and medullary cytosols, indicative of lead's renotoxic mechanism. Kidney cytosols from rats injected with lead acetate (114 mg/kg, 3 consecutive daily injections) were prepared, solubilized and separated by two-dimensional electrophoresis (2-DE). Stained gels were digitized and protein patterns analyzed using the Kepler® 2D Gel Analysis System. An average of 727 protein spots were resolved and matched to the cortex cytosol reference pattern and 716 in the medulla. Lead exposure significantly ($P<.001$) altered the abundance (either ↑ or ↓) of 75 proteins in the cortex and only 12 in the medulla. Eleven of the proteins altered in the protein patterns were conclusively identified and lead-effects compared. None of these proteins was preferentially altered in the medulla. Several of the cortical proteins altered by lead were unchanged in the medulla while others underwent similar but lesser alterations. The effected protein types ranged from Yp GST to stress proteins to enzymes of urea and pentose metabolism. Alterations in expression of phosphorylated proteins also showed a preferential cortical effect. These results support the utility of electrophoretic biomarkers in screening and mechanistic studies. Supported by AFOSR Grant #s F49620-96-1-0156 and F49620-96-1-0074.

1862 ULTRASTRUCTURAL AND ELECTRON PROBE X-RAY MICROANALYSIS MAPPING OF PROXIMAL TUBULES OF RAT KIDNEY FOLLOWING LOW-LEVEL LEAD INGESTION.

A S Osman[1], A LeFurgey[2], P Ingram[3], N Shaaban[4], and M B Abou-Donia[1]. [1]*Dept. of Pharmacology and Cancer Biology,* [2]*Dept. of Cell Biology, Duke University Medical Center, Durham, NC,* [3]*Research Triangle Institute, RTP, NC,* [4]*Alexandria University, Alexandria, Egypt.*

Young male Sprague Dawley rats were given 0.2% lead acetate in drinking water for 18 weeks. Control rats received distilled water. At end of treatment, kidneys underwent ultrastructural study by conventional transmission electron microscopy (CTEM). *In situ* cryofixation of the kidney was carried out using the metal-mirror method. Electron probe x-ray microanalysis (EPXMA) mapping was performed to determine simultaneously the intracellular elemental (including lead) content and distribution in the renal cortex proximal tubules. Although lead treatment did not produce signs of overt toxicity, treated rats exhibited 10% decrease in weight gain compared to control. CTEM examination of lead-treated rats revealed intranuclear inclusion bodies within the epithelial cells of proximal tubules, and accumulation of lysosomes. Some cells also showed dilation of the intercellular spaces and loss of microvilli. EPXMA images indicated that lead was only detected within intranuclear inclusion bodies. No lead was present in the cytoplasm, lysosomes, or mitochondria. The K/Na ratio was normal (10/1) and other intracellular elemental concentrations were also normal. Although the epithelial cells lining the proximal tubules from rats exposed to subclinical low-level lead appeared physiologically normal, they exhibited subtle cellular alterations. 1) The ultrastructural changes detected may be precursors for further, more severe toxicity. 2) The formation of the pathognomonic intranuclear inclusion bodies suggests that the nucleus is an early target for lead toxicity and that lead may have an influence on gene expression.

1863 ASSESSMENT OF A VANCOMYCIN (VAN)-INDUCED CELL PROLIFERATIVE EFFECT IN RENAL CELL CULTURES.

D W King and M A Smith. *Toxicology Program, The University of Texas School of Public Health, Houston, TX.*

Previous work in our laboratory has demonstrated increased kidney weights within 48 hours post-dosing of VAN (450 and 750 umol/kg). This increase in kidney weight is the result of an increase in renal protein, water, and phospholipid content. Previous *in vitro* studies performed in our laboratory demonstrated a VAN-induced increase in cell number and total protein content within 24 hrs following exposure to 2.5 & 5 mM VAN in primary cultures of renal cortical epithelial cells. To ensure that the effect was indeed due to an epithelial cell effect and not due to possible fibroblast contamination, these experiments were repeated and confirmed in the LLCPK$_1$ porcine renal proximal tubule epithelial cell line. The purpose of these experiments was to investigate the effects of VAN(1, 2.5, & 5 mM) on cell proliferation. Evidence of a proliferative effect was observed histochemically using BrDU immunohistochemical staining in primary renal cell cultures after 24 hrs of VAN exposure. ^{3}H-Thymidine incorporation assays were also performed to determine if a VAN-induced cell proliferative/ hyperplastic effect could be detected; however, these studies provided inconclusive results. These data suggest that a VAN-induced cell proliferative effect may exist and should be further investigated. (Supported by NIEHS Training Grant T32-ES-07290 [DWK] and GM47549[MAS])

1864 EFFECT OF PROBENECID (PRO) ON THE ATP CONTENT OF LLC-PK$_1$ CELLS.

D Wu and S Ford. *Pharmaceutical Sci., St. John's University, Jamaica, NY.*

Previous studies have shown that probenecid is toxic to cultured kidney cells (Toxicologist 12:372). The present study was designed to examine the relationship between cytotoxicity and intracellular ATP content in LLC-PK$_1$ cells treated with PRO. LLC-PK$_1$ cells were grown in 35 mm plastic culture

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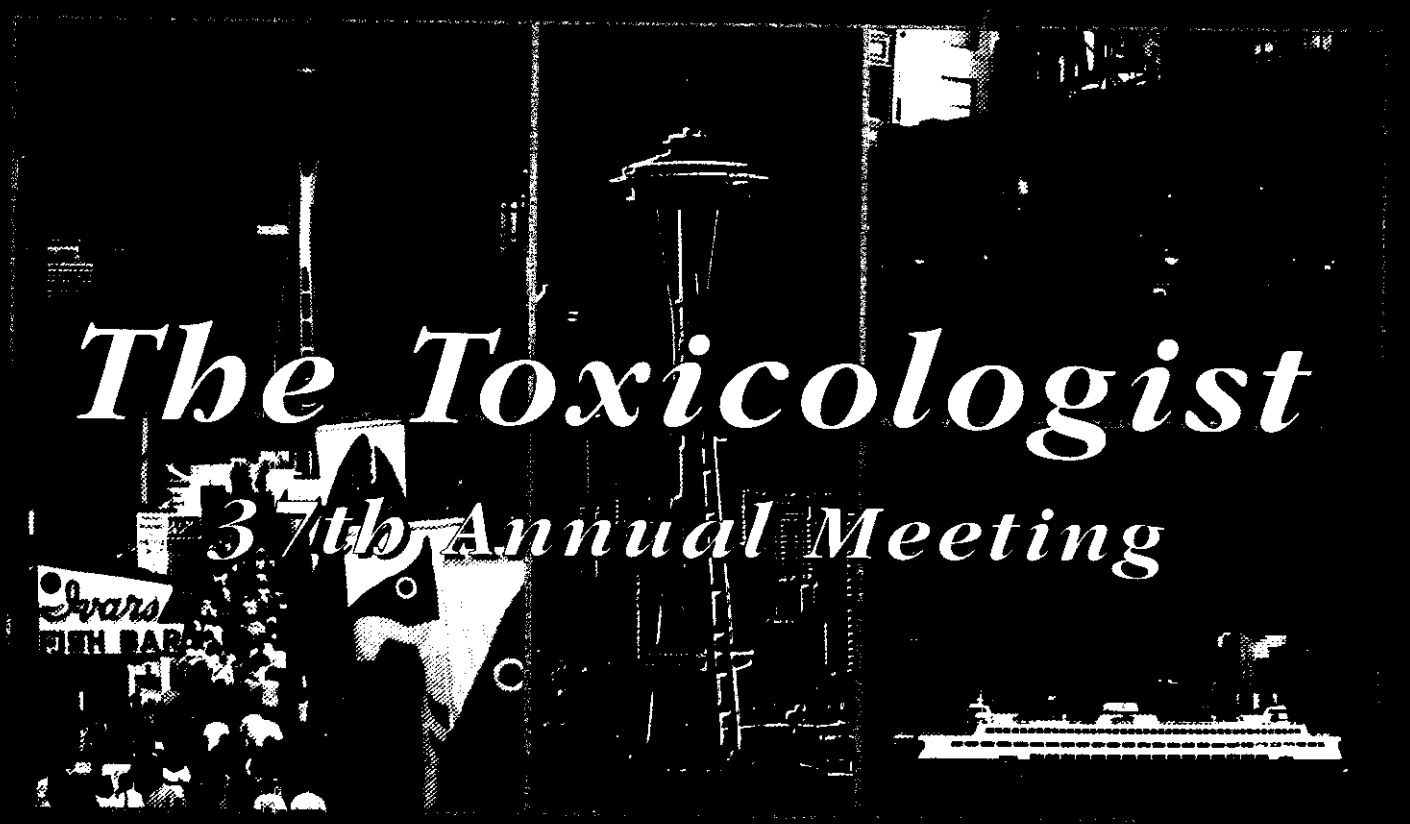

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster / discussion, workshop, roundtable, and poster sessions of the 37th Annual Meeting of the Society of Toxicology, held at the Washington State Convention Center, Seattle, Washington, March 1-5, 1998.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 407.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 433.

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