to H_2O_2 or menadione, a quinone compound which generates reactive oxygen species continuously. MIP-2 mRNA levels were significantly increased after 1 h and 4 h exposures to H_2O_2 (500 μM) or menadione (50 μM). Co-treatment of macrophages with the transcriptional inhibitor actinomycin D (5 μg/ml) eliminated the H_2O_2- and menadione-induction of MIP-2 mRNA, implicating a role for transcriptional activation of MIP-2 gene expression. Genomic cloning of the rat MIP-2 gene 5′-flanking region allowed identification of consensus NF-κB and AP-1 binding sites. Gel-mobility shift assays revealed that NF-κB binding to the MIP-2 promoter/enhancer sequence was induced by H_2O_2, but not menadione. The half-life of MIP-2 mRNA transcripts was also increased in response to H_2O_2 treatment, but was not influenced by menadione. These observations indicate that MIP-2 gene expression is subject to differential control dependent on the initial source of the oxidative stress at both transcriptional and post-transcriptional levels.
(Supported by ES00002, ALA, and a Parker B. Francis Fellowship)

1706 COCAINE ACTS AS A PARTIAL AGONIST AT MUSCARINIC RECEPTORS IN TRACHEAL SUBMUCOSAL GLAND CELLS.

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The effects of cocaine on airway chloride secretion were examined using swine tracheal submucosal gland cells in primary culture to measure short-circuit current (Isc) or whole-cell transient inward currents. Cocaine (0.3–3 mM) induced concentration-dependent inhibition of Isc and inward currents in some experiments and cocaine evoked increases in Isc and inward currents in other studies. Cocaine shifted the concentration-response curve to the right for ACh (0.1–100 μM) induced Isc; but did not inhibit the maximal response, suggesting that cocaine acts as a competitive antagonist at muscarinic receptors. Cocaine also inhibited ACh-induced potentiation of whole-cell inward currents. Atropine did not affect basal Isc, but increased the inhibitory action of cocaine on Isc, suggesting that there is a stimulatory action of cocaine that was blocked. The molecular structures of cocaine and atropine were found to be similar. Both cocaine and atropine have a tropane ring. Based on space-filling models, the distance between the amide group and one carbonyl group of cocaine is similar to that of ACh. Therefore, we suggest that cocaine is a partial agonist at muscarinic receptors. This behavior of cocaine occurs in muscarinic stimulation in addition to its local anesthetic effect via blockade of cation channels. (Supported by American Lung Assoc. of MS, HL55547 and DA 05094)

1707 ANTIOXIDANT PROPERTIES OF THE PINEAL NEUROHORMONE MELATONIN IN CELL-FREE AND LUNG CELL MODEL SYSTEMS.

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The pineal hormone melatonin exhibits pluripotent biological activities, including modulation of the endocrine, neuroendocrine, and immune systems. Recent evidence has also attributed an antioxidant property to this neurochemical. We have investigated direct quenching of reactive oxygen species by melatonin in cell-free and cell models via electron spin resonance (ESR) studies. Cell-free studies yielded the following information: 1) melatonin inhibited superoxide anion formation with a rate constant of 1.25×10^3 $M^{-1}s^{-1}$ in reaction with xanthine/xanthine oxidase; 2) melatonin did not inhibit hydroxyl radical generation in a Fenton reaction; 3) melatonin quenched singlet oxygen produced in a rose bengal photodynamic reaction. On the other hand, melatonin treatments of stimulated alveolar macrophages at physiologic nanomolar concentrations resulted in a dramatic inhibition of hydroxyl radical formation (IC-50 = 0.38 nM), moderate inhibition of hydrogen peroxide formation, and no effects on production of superoxide anion. Interestingly, melatonin also inhibited oxidative DNA strand damage/formation of 8-deoxyguanine adducts, as detected by gas chromatography-mass spectrometry, and lipid peroxidation as detected by ELISA, biological effects attributed to inhibition of hydroxyl radical and singlet oxygen, respectively. Ongoing studies are further investigating modulation of DNA transcription factor activities by melatonin. [Support from NIOSH and USACEHR]

1708 EFFECTS OF BLEOMYCIN ON AN IN VITRO COCULTURE SYSTEM OF HUMAN BRONCHOEPITHELIAL CELLS AND LUNG FIBROBLASTS.

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Co-cultures of human pulmonary epithelial cells and lung fibroblasts, representing two cell types of central regulatory potential in (chronic) lung disease, are a useful in vitro model to study the mechanisms of chemical-induced pulmonary lesions such as fibrosis. Membrane cultures of human bronchoepithelial cells (BEAS-2B) were pretreated with bleomycin (BLM, 0–5000 ng/ml), an antineoplastic antibiotic with known fibrotic potential, for 20 h and were further co-cultivated with human lung fibroblasts (Wistar-38) for 48 h. Gene expression of procollagens type I and III as well as of various proinflammatory / fibrogenic mediators was determined by RT-PCR. In the presence of BLM-treated epithelial cells, gene expression of IL-6 and MCP-1 was considerably increased in fibroblasts in a dose-related manner, whereas steady-state mRNA levels of both procollagens were only slightly enhanced. Likewise, bronchoepithelial cells, in response to bleomycin, also exhibited a dose-dependent enhancement in gene expression of the proinflammatory mediators TNF α, IL-6, MCP-1 and GM-CSF and, to a much lesser extent, of the fibrogenic growth factors TGF β2 and PDGF B. In summary, BLM pretreatment induced bronchoepithelial cells to react with increased gene expression of multiple factors contributing to (chronic) inflammation and fibrogenic processes and, in addition, to mediate enhanced fibroblast activity.

1709 COMPARISON OF AMIODARONE CYTOTOXICITY IN DIFFERENT ISOLATED HAMSTER LUNG CELL TYPES.

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Amiodarone (AM), a potent antidysrhythmic agent, can cause life-threatening pulmonary fibrosis. Identification of target cells for AM toxicity, and understanding the basis for their selectivity, should clarify initiating events of AM-induced pulmonary toxicity. Bronchoalveolar lavage of male golden Syrian hamster lungs, and protease digestion to release cells, followed by centrifugal elutriation and density gradient centrifugation resulted in preparations enriched with alveolar macrophages (98%), alveolar type II cells (75–85%) and non-ciliated bronchiolar epithelial (Clara) cells (35–50%). Cytotoxicity, measured by 0.05% trypan blue dye uptake, was greater ($p < 0.05$; $n = 4$) in the Clara cell fraction than in other fractions incubated with 50 μM AM for 36 h. However, cytotoxicity was greatest ($p < 0.05$; $n = 5$) in the alveolar macrophage fraction following incubation with 100μM AM for 36 h or 200 μM AM for 12–36 h. HPLC analysis demonstrated no difference in the amount of drug accumulated during 24 h of incubation with 50 μM AM amoung enriched cell preparations. In contrast, alveolar macrophages accumulated the most amount of drug when incubated with 100 μM AM. AM-induced alveolar macrophage activation, indicated by nitroblue tetrazolium conversion to formazan, increased concurrently with decreased cell viability, and was AM concentration-dependent. These findings demonstrate that selective sensitivity of alveolar macrophages to 100 μM AM involves drug accumulation and cell activation. (Supported by Medical Research Council of Canada Grant No. MT- 13257).

1710 ENHANCED CELL SURVIVAL IN NORMAL HUMAN BRONCHIAL EPITHELIAL CELLS TREATED WITH HYDROGEN PEROXIDE.

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Bronchial epithelial cells (BEC) are constantly exposed to environmental agents that can result in the production of reactive oxygen species (ROS) via direct and/or indirect mechanisms. Such ROS can cause DNA damage, including strand breaks that have been associated with the induction of cell cycle checkpoints and arrests. Paradoxically, however, airway epithelial cells frequently appear to undergo enhanced proliferation in a background of ROS exposure *in vivo*, as evident by bronchial epithelial cell (BEC) hyperplasia. Based on the literature, intracellular ROS, particularly H_2O_2, conceivably may form a part of a signal transduction cascade that leads to promitogenic responses. In this study, BEC were primed with a low concentration of H_2O_2 (0.1 μM) followed by subsequent treatments with H_2O_2 at concentrations ranging from 0.1 to 100 μM. Control cultures consisted of BEC that did not

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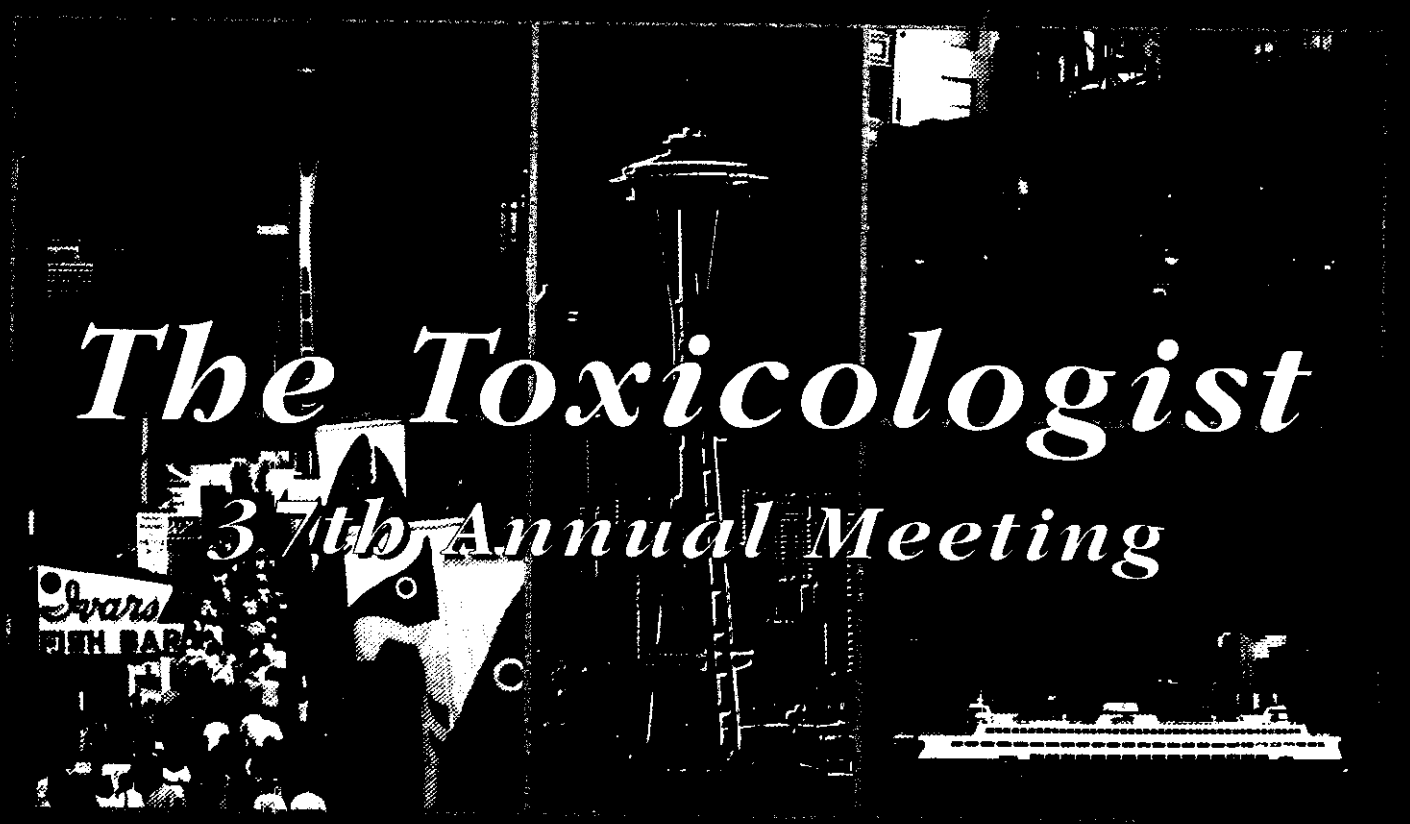

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Preface

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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