drone and an estrogen compound, β-estradiol. One of the six patients showed significantly elevated LHR, compared to normal controls, when basophils were challenged with progesterone, 5-β-pregnanediol, or norethindrone, at 1 month and at 3 months after an anaphylactoid episode. LHR by estradiol in this patient was not elevated above that of normal controls. Patient sera were tested for anti-progesterone antibodies, using isotype-specific indirect ELISA tests with progesterone-BSA antigen-coated plates. Controls included tests for antibody to BSA, the protein carrier for the progesterone hapten. The sera of all 6 patients contained progesterone-specific IgG antibodies that showed binding to BSA-progesterone, without binding to unconjugated BSA. Three of the 6 patients contained progesterone-specific IgE antibodies. The results suggest that the premenstrual syndrome is associated with immune responses, some of which are IgE-mediated. This is the first report of IgE anti-progesterone antibodies in women with progesterone-associated hypersensitivity-like symptoms.

1024 OCCUPATIONAL EXPOSURE TO AEROSOLIZED EGG ALLERGENS AT AN EGG PROCESSING FACILITY.

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Inhaled proteins are occupational allergens which cause IgE-mediated occupational asthma (OA) in egg production workers (Ws). Raw and processed egg particles become airborne during processing. To evaluate occupational ambient exposure to aerosolized egg, we quantitated total protein and specific egg allergens: ovalbumin (OVA), ovomucoid (OVOM), & egg lyzozyme (LYS), in air samples taken at a facility with 95 exposed Ws. Aerosol exposures were monitored using 37-mm closed-face cassettes with polyethylene-supported Teflon™ filters and personal sampling pumps, with air flow of 2 l/min., for an 8-hour shift. Filter protein was eluted in PBS, .05% Tween 20, pH 7.4. BCA tests (Pierce) were used to measure total protein; specific allergens were measured by competitive inhibition and sandwich EIAs. The mean values determined for total protein in $\mu g/m^3$ air sample for different jobs/departments were: transfer, 644; breaking, 255; pasteurization, 32; dryer, 91; egg white packaging, 426; egg yolk packaging, 46; sanitation, 9.3. The percent of protein attributable to specific egg allergens also showed variation depending on the area sampled: ovalbumin, 50 – 99%, ovomucoid, 3 – 25%, lysozyme, <.01 – 10%. In stationary paired samples, the mean respirable/total protein ratio was 322/607 $\mu g/m^3$. A control referent plant showed a maximum of 41 $\mu g/m^3$ protein with no detectable specific egg protein. The results indicate that OVA, which comprises 54% of egg protein was the predominant airborne antigen. Air sampling for egg protein can be useful to identify those locations where workers are exposed to high concentrations and where additional controls might be implemented.

Supported by NIOSH OMB 0990–0115

1025 THE MOLECULAR BIOLOGY OF METAL CARCINOGENESIS.

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This symposium will explore recent advances in our understanding of the cellular/molecular mechanisms of metal carcinogenesis and the molecular biology of metal carcinogenesis. Dr. Loeb will discuss involvement of oxygen radicals in cancer and analyze types/frequencies of mutations produced in vitro by reactive oxygen species generated by metals associated with human cancers. Dr. Costa will discuss epigenetic mechanisms of nickel carcinogenesis, including cell transforming activities of insoluble nickel compounds and their ability to induce chromatin condensation and fix it via hypermethylation of cytosines in DNA, inactivating tumor suppressor/senescence genes. Dr. Landolph will describe arsenic, nickel, and chromium-induced neoplastic transformation of 10T1/2 mouse embryo cells and anchorage independence in human fibroblasts without mutation to ouabain-6-thioguanine resistance and discuss increased levels of c-myc RNA/protein and stabilization of c-myc RNA in lead chromate transformed 10T1/2 cell lines, RNA differential display analyses of chromium/nickel transformed 10T1/2 cell lines, and oncogenes overexpressed and tumor suppressor genes underexpressed in metal-transformed 10T1/2 cell lines. Dr. Karin will discuss mechanisms of AP-1 - mediated tumor and anti-tumor promotion. As + 3 activation of c-fos and c-jun downstream of MAP kinase kinase JN-KK, therefore AP-1 activation, and that anti-tumor promoters inhibit AP-1 activity.

1026 THE INVOLVEMENT OF OXYGEN FREE RADICALS IN CANCER.

T Newcomb, A Jackson and L A Loeb. *Departments of Pathology and Biochemistry, University of Washington, Seattle, WA.* Sponsor: J R Landolph.

The generation of oxygen reactive species has been considered to be one of the most frequent causes of DNA damage. However, an evaluation of their role in carcinogenesis has been hindered by the diverse DNA lesions they cause. We analyzed the frequency and types of mutations produced *in vitro* by reactive oxygen species generated by metals that are associated with human cancers. Our evidence indicates: 1) the most frequent mutations are C ⇒ T transitions and we have recently identified one lesion, 5-OH-dC that causes these mutations; 2) G ⇒ C transversions result from damage by singlet oxygen; 3) G ⇒ T transversions result from 8-OH-dG due to mispairing with dATP; 4) dATP is also misincorporated opposite apurinic sites; and 5) CC ⇒ TT mutations are diagnostic of damage by oxygen free radicals or UV-irradiation. We have established a PCR-based assay that can detect one CC ⇒ TT substitution among 10^7 copies of the gene encoding DNA polymerase-β. We will determine if these mutations accumulate during tumor progression. A decrease in the rate of metal induced mutagenesis by antioxidants could prevent the clinical occurrence of metal associated cancers.

1027 EPIGENETIC MECHANISMS OF NICKEL CARCINOGENESIS.

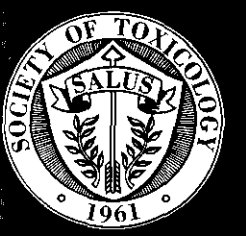
M Costa. *Department of Environmental Medicine, New York University Medical Center, New York, NY.*

Certain carcinogenic particulate nickel compounds, such as crystalline nickel sulfide and nickel subsulfide display much higher activities than water-soluble nickel compounds because these particles are phagocytized by cells and produce very high concentrations of nickel inside the cell in contrast to water-soluble nickel salts which do not readily enter cells. Carcinogenic nickel compounds are not highly mutagenic and do not induce a high degree of DNA damage. However, tumor suppressor and senescence genes are inactivated in their transcription in nickel-transformed cells. Using a model system of transgenic cell lines to study the mechanism of transcriptional inactivation by nickel compounds, it was found that carcinogenic nickel compounds induce inactivation of transgenes placed near heterochromatin by a Ni-enhanced chromatin condensation which was subsequently fixed in a more condensed state by DNA cytosine hypermethylation. We will describe the mechanism by which nickel produces DNA hypermethylation addressing the question of whether carcinogenic nickel compounds induce only localized DNA hypermethylation near heterochromatic regions or are also capable of inducing a generalized cytosine hypermethylation of genomic DNA. These experiments are being conducted by studying wild-type and nickel-resistant cells and cells treated with carcinogenic nickel compounds, as well as in nickel-transformed cells. These studies show that carcinogenic nickel compounds act on the immortalization process by epigenetic mechanism involving DNA hypermethylation and inactivation of transcription of senescence and other tumor suppressor genes. Mounting experimental evidence in the literature points to the importance of DNA hypermethylation and inactivation of tumor suppressor genes as an important event in human carcinogenesis.

1028 MOLECULAR BIOLOGY OF CHROMIUM AND NICKEL-INDUCED NE-OPLASTIC TRANSFORMATION OF 10T1/2 MOUSE EMBRYO CELLS.

J R Landolph, L Ozbun, and A Verma. *Depts. of Mol. Microbiology/Immun., Pathol., and Mol. Pharm./Toxicol., USC Cancer Center, School of Medicine, Univ. of Southern Calif., Los Angeles, CA.*

Carcinogenic arsenic, chromium, and nickel compounds induced morphological and neoplastic transformation in 10T1/2 mouse embryo cells without mutation to ouabain resistance (OR), or to 6-thioguanine resistance (6TGR) in CHO cells (lead chromate), and induced transformation to anchorage independence (AI) in human diploid fibroblasts (HDF). Nickel-induced AI in HDF was blocked by inhibitors of arachidonic acid (AA) release (dexamethasone) and metabolism (aspirin) suggesting oxygen radicals derived from the AA cascade might activate oncogenes and inactivate tumor suppressor genes during nickel-induced AI. Lead chromate transformed 10T1/2 cell lines had 4–8-fold increased levels of c-myc RNA, increased half-lives of a fraction of c-myc RNA, and 2-fold increased steady-state levels of c-myc protein,



The Toxicologist

Volume 36, No. 1, Part 2,
March 97

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The Toxicologist

An Official Publication of the Society of Toxicology

and

Abstract Issues of

Fundamental and Applied Toxicology

An Official Journal of the Society of Toxicology

Published by Academic Press, Inc.

Abstracts of the
36th Annual Meeting
Volume 36, No. 1, Part 2,
March 97

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster / discussion, workshops, roundtables, and poster sessions of the 36th Annual Meeting of the Society of Toxicology, held at the Cincinnati Convention Center, Cincinnati, Ohio, March 9-13, 1997.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 371.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 395.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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