



1171

APPROACHES TO THE ANALYSIS OF ENDOGENOUS DNA DAMAGE IN PEOPLE.

L. J. Marnett and J P Plataras. *Department of Biochemistry, Center in Molecular Toxicology, and the Vanderbilt Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA.*

Characterization of the sources of DNA damage in human beings is critical for identifying the causes of genetic diseases. A compendium of DNA damage products indicates that endogenous metabolic processes play a very significant role in genomic alteration. For example, malondialdehyde is a naturally occurring product of lipid peroxidation and prostaglandin biosynthesis that is mutagenic and carcinogenic. It reacts with DNA to form adducts to deoxyguanosine and deoxyadenosine. The major adduct to DNA is a pyrimidopurine called M₁G. This adduct is highly mutagenic in *E. coli* and has been detected in liver, white blood cells, pancreas, and breast from healthy human beings at levels ranging from 1 - 120 per 10⁸ nucleotides. Efforts are underway to develop high throughput methods for quantitation of MDA in population-based studies. Several different assays for M₁G have been described that are based on mass spectrometry, ³²P-postlabeling, or immunochemical techniques. Each technique offers advantages and disadvantages based on a combination of sensitivity and specificity. Recent advances in the application these techniques to the analysis of M₁G will be discussed as a prototype for the analysis of other endogenous DNA adducts.



1172

IMMUNOLOGIC METHODS FOR MEASURING DNA ADDUCTS: APPLICATIONS TO MOLECULAR EPIDEMIOLOGIC STUDIES.

R. M. Santella. *Division of Environmental Health Sciences, Columbia School of Public Health, New York, NY, USA.*

Measurement of carcinogen-DNA damage in humans can provide important information on individual exposure to various environmental, lifestyle, or occupational carcinogens. Polyclonal antisera and monoclonal antibodies recognizing specific types of DNA damage have high sensitivity and can easily analyze large numbers of samples. We are currently using an anti-serum recognizing polycyclic aromatic hydrocarbon (PAH)-DNA in a competitive enzyme-linked immunosorbent assay (ELISA) to analyze lymphocyte DNA adducts in a breast cancer case-control study. The same antiserum is being used for immunoperoxidase staining of breast tissue sections to determine the correlation between target and surrogate tissue adduct levels. Investigation of the relationship between adducts and genotype for glutathione S-transferases M1 and P1 will help in understanding interindividual variation in DNA damage. Immuno-histochemical analysis of exfoliated oral and bladder cells for 4-aminobiphenyl (4-ABP)- and PAH-DNA and oxidative DNA damage (8-hydroxyguanosine) demonstrated elevated levels of damage in smokers compared to nonsmokers, suggesting these are good markers of exposure. Studies on the correlation between DNA damage and mutations in p53, a tumor suppressor gene, demonstrated an increased risk for mutant p53 in subjects with higher levels of aflatoxin B₁ or 4-ABP-DNA adducts, suggesting the importance of adducts in the etiology of cancer development. Finally, adduct measurements are also useful as intermediate biomarkers in intervention studies. For example, we recently completed an antioxidant vitamin intervention in smokers in which the endpoint is modulation of DNA damage in lymphocytes and exfoliated oral and bladder cells. Demonstration that an intervention can modulate a biomarker on the pathway to cancer development should simplify the testing of new chemopreventive agents.



1173

MOLECULAR MARKERS OF BIOLOGICAL EFFECT - USE AS MEASURES OF RETROSPECTIVE CUMULATIVE EXPOSURE AND AS PREDICTORS OF HUMAN HEALTH EFFECTS.

W. L. Bigbee. *Center for Environmental and Occupational Health and Toxicology, University of Pittsburgh, Pittsburgh, PA, USA.*

The tools provided by modern molecular biology and genetics, together with ever more sensitive and sophisticated analytical instrumentation, have allowed the development of powerful new markers of early biological effects relevant to the molecular etiology of human disease. These effect biomarkers, representing both cytogenetic and molecular genetic methods, have found useful application in recent molecular epidemiological studies both for assessing the biological impact of distant and/or cumulative exposures to

chemical and physical agents as well as predicting, and molecularly characterizing, subsequent clinical disease. Examples from the contemporary literature will be used to illustrate these concepts and the current "cutting edge" of laboratory methods and molecular epidemiological study design. While these tools are presently best developed in cancer epidemiology, examples using other chronic disease endpoints and adverse reproductive effects will also be presented. Finally, the presentation will include a discussion of rapidly emerging techniques and scientific concepts that represent the next generation of biological markers that promise to offer increased sensitivity and specificity, early detection of preclinical disease, population screening for identification of susceptible groups, and assessment of individual risk of disease.



1174

LINKING BIOMARKERS OF BIOLOGICALLY EFFECTIVE DOSE AND EARLY BIOLOGIC EFFECT TO DISEASE RISK IN EPIDEMIOLOGIC STUDIES.

P. A. Schulte¹ and N. Rothman². ¹*NIOSH-Taft Labs, Cincinnati, OH;* ²*Division of Cancer Epidemiology and Genetics, NCI, Bethesda, MD, USA.* Sponsor: R. M. Santella.

In order to understand the relevance of biomarkers of biologically effective dose and early biologic effects in a broad public health context, it is critical to understand the biomarker-disease relationship. Although preliminary work can be carried out for some biomarkers in case-control studies, the potential for disease bias will always raise a concern about results from these studies. As such, prospective cohort studies carried out on large, generally healthy populations are the optimal approach to study the relationship between biomarker levels and disease risk. In these studies, biologic samples are collected from a defined population and banked for later analysis. The cohort is followed forward in time; subjects who develop disease are identified, and premorbid biomarker levels in these cases are then compared with those in unaffected subjects. Often, a nested case-control approach is used. Samples from cases and only a sample of the controls are analyzed, which considerably reduces the laboratory requirements and costs. These studies allow calculation of the relative risk, which provides an estimate of the increased risk in disease for a given level of a biomarker, and the etiologic fraction, which estimates the proportion of disease reflected by the biomarker. The consistent results across several, small cohort studies showing a positive relationship between chromosomal aberration levels in peripheral lymphocytes and subsequent cancer incidence or mortality suggest that at least some biomarkers of early biologic effect will prove to be relevant for predicting cancer risk. There will soon be over a million subjects with blood samples banked in cohort studies in the U.S., Europe, and Asia. These studies will provide striking opportunities for the evaluation of the relationship between a wide range of biomarkers and disease risk over the coming years.



1175

TOXICOLOGY FOR KIDS: A HOW TO GUIDE FOR TOXICOLOGISTS.

G. S. Yost¹ and C. A. McQueen². ¹*Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT, USA* and ²*Department of Pharmacology and Toxicology, University of Arizona, Tucson, AZ, USA.*

SOT has recognized the importance of education in the science of toxicology for students in grades K-12. While many members of SOT are interested in becoming involved in K-12 education, there is much uncertainty in what to do and how to do it. The Education Committee and its K-12 Subcommittee are committed to activities that will enhance the efforts of SOT members in their efforts. Thus, the K-12 Subcommittee has enlisted the help of several prominent scientists and educators to provide a program focused on the practical aspects of outreach programs with kids. The purpose of the workshop is to give SOT members the philosophical approaches and specific educational tools that are effective in classroom presentations. Specific hands-on demonstrations of proven techniques will be provided at the workshop.



1176

TOXICOLOGY CAN TURN KIDS ON TO SCIENCE.

N. Biggart. *Bonita Vista High School, El Cajon, CA, USA.* Sponsor: G. S. Yost.

Toxicology is an excellent discipline with which to engage the interest of high school students because of two characteristics: it is relevant to students'

All Official Journal of the
Society of Toxicology
Supplement

20th

ANNUAL MEETING

TOXICOLOGICAL SCIENCES

Formerly Fundamental and Applied Toxicology

The Toxicologist



Oxford University Press

Volume 48, Number 1-S, March 1999

The Toxicologist

An Official Publication of the Society of Toxicology

and

Abstract Issues of

TOXICOLOGICAL SCIENCES

An Official Journal of the Society of Toxicology

Published by Oxford University Press, Inc.

*Abstracts of the
38th Annual Meeting
Volume 48, Number 1-S
March 1999*