hydroxycatechols seem to form mainly stable bulky adducts whereas the carcinogenic 4-hydroxylated metabolites primarily alkylate the N-7 position of guanine generating apurinic sites. The equine estrogens present in the popular estrogen replacement formulation Premarin® (Wyeth-Ayerst) can be metabolized to primarily 4-hydroxylated products. In contrast to the endogenous catechol estrogens, the 4-hydroxyequine estrogens autoxidize to semiquinone radicals and o-quinones without the need for oxidative enzyme catalysis. Both 4-hydroxyequilin and 4-hydroxyequilenin form the same highly unusual cyclic adducts with DNA. Several different types of lesions result including, bulky stable adducts with guanine and cytosine and apurinic sites resulting from adenine alkylation. Finally, 4-hydroxyequilenin in particular causes significant oxidative damage to guanine and adenine residues as well as damage to the phosphate/sugar backbone of DNA. These data suggest that DNA damage mediated by endogenous and/or exogenous catechol estrogens could contribute to the carcinogenic effects of estrogens in vivo. (Supported by CA73638-01.)

1167 QUINONE-THIOETHER MEDIATED TOXICITIES.

T J Monks and S S Lau. *Div. of Pharmacology & Toxicology, College of Pharmacy, Univ. of Texas at Austin, TX, USA.*

Conjugation of reactive electrophiles, such as quinones, with glutathione (GSH) is frequently associated with detoxication. However, quinol-GSH conjugates retain the ability to redox cycle, and the reactivity of the corresponding quinone-thioether often exceeds that of the parent quinone. Indeed, quinone-thioether-mediated DNA damage (including mutations [base substitutions/deletions] and single-strand breaks), growth arrest, cell transformation, and cell death (necrosis and apoptosis) are all linked to the generation of reactive oxygen species. Conjugation with GSH is usually efficiently coupled to the export of the conjugate from the cell, and limits the potential toxicity of quinol-GSH conjugates. In contrast, GSH conjugates are transported into cells via either the activity of an intact GSH transporter, or as the corresponding cysteinylglycine and cysteine conjugates following metabolism by γ -glutamyl transpeptidase (γ -GT) and dipeptidases. Cells that express either γ -GT or an intact GSH transporter will therefore be exposed to the potential toxic effects of these conjugates. Tissues susceptible to quinol-GSH conjugate induced toxicities share interesting physiological similarities. For example, γ -GT is frequently located in cells that separate the circulation from a second fluid filled compartment, such as occurs in the blood-urine (renal proximal tubule cells) and blood-brain (brain endothelial cells) barriers. Quinol-GSH conjugates are nephrotoxic, nephrocarcinogenic, and neurotoxic. In the latter case however, access to the brain appears to be mediated by an intact GSH transporter, and not by γ -GT. Similar physiological barriers exist within the body and may provide additional sites for the toxicity of these conjugates. (ES07359, ES 07247, CA58036, DA10832, GM 39338)

1168 QUINONE-THIOETHERS AND PARKINSON'S DISEASE.

G Dryhurst, X-M Shen, H Li, J H Han, L Gu, Z Yang, and F-C Cheng. *Department of Chemistry and Biochemistry, University of Oklahoma, Norman, OK, USA.* Sponsor: J L Bolton.

The characteristic motor symptoms of PD (tremor, rigidity, akinesia) are caused by the degeneration of nigrostriatal dopamine (DA) neurons. The pathological processes occur in the neuromelanin-pigmented cell bodies of these neurons in the substantia nigra pars compacta (SNc) and include a defect in mitochondrial respiration at the level of complex I and decreased α -ketoglutarate dehydrogenase. A massive loss of glutathione (GSH) is the earliest known change in the parkinsonian SNc that slightly precedes the complex I defect. Another change in the SNc of PD brains is increased activity of γ -glutamyl transpeptidase. Based on these observations and information drawn from studies of the dopaminergic neurotoxicity evoked by MPTP, methamphetamine and ischemia-reperfusion, a new mechanism will be discussed based on reactions between DA-o-quinone and cysteine. The intraneuronal reaction between DA-o-quinone and CySH is proposed to form cysteinyl conjugates of DA that are further easily oxidized to a number of dihydrobenzothiazines (DHBTs) and benzothiazines (BTs). These DHBTs/BTs include putative intraneuronal metabolites that can be accumulated by mitochondria and evoke irreversible inhibition of complex I and α -KGDH. These effects involve oxidation of DHBTs and BTs by a constituent of the inner mt membrane to give highly electrophilic intermediates that covalently bind to -SH residues of NADH-coenzyme Q1 reductase and α -KGDH thus evoking irreversible inhibition.

1169 BIOLOGIC MARKERS IN MOLECULAR EPIDEMIOLOGY: MEASURES OF EXPOSURE AND RISK FOR CANCER DEVELOPMENT.

R M Santella[1] and D G DeBord[2]. [1]*Columbia School of Public Health, New York, NY, USA and* [2]*National Institute for Occupational Safety and Health, Cincinnati, OH, USA.*

Although biomarkers have been used for sometime in epidemiology, recent advances in molecular biologic techniques have made it possible to detect biologic changes at low levels of exposure. Biomarkers can be used to identify exposures, effects of those exposures, and populations that may be at increased risk. Measurement of DNA adducts from polycyclic aromatic hydrocarbons, aflatoxin, and alkylating agents have been used to monitor exposure to these agents in smokers, workers, and those with environmental exposure. Lipid peroxidation produces high levels of malondialdehyde-DNA adducts which are highly mutagenic. Oxidative DNA damage is also present at high levels. Thus, DNA damage from endogenous sources may be an important factor in tumor development. Data on the relationship between DNA damage (or protein damage as a surrogate) and risk for cancer have demonstrated that these assays can predict development of disease in populations exposed to aflatoxin. Genetic susceptibility factors related to ability to metabolize carcinogens influence DNA damage levels and cancer risk. Biomarkers of effect measure mutations (HPRT or glycophorin A) or cytogenetic damage and are useful to help bridge the continuum of exposure to disease. Many of the biomarkers of exposure and early effects are reversible and can be used as tools to monitor reductions in workplace exposure or the efficacy of chemoprevention studies. The rapid expansion of large banks of stored blood samples will make possible nested case-control studies evaluating the relationship between biomarkers and disease risk and gene-environment interactions.

1170 THE RELATIVE CONTRIBUTION OF EXOGENOUS AND ENDOGENOUS EXPOSURES OF HUMANS TO CARCINOGENS AS REFLECTED BY DNA AND PROTEIN DAMAGE.

P B Farmer [1], Y Guichard[1], G D D Jones[2], E Martin[1], V I C Oreffo[1], R Singh[1], and D E G Shuker[1]. [1]*MRC Toxicology Unit and* [2]*CMHT, University of Leicester, Leicester, UK.*

DNA and protein adducts are now widely accepted as valid monitors of exposure to genotoxic compounds. In the case of hepatocellular carcinoma, biomarkers of exposure to aflatoxin B1 including DNA adducts proved to be highly predictive of tumour outcome in humans. Correlations between low dose exposures and DNA adduct formation in target organs have been observed for a number of carcinogens in experimental systems. However, in a recent study of N©nitrosodiethylamine in 3 inbred mice strains we showed that within strains there was a strong correlation between DNA adduct levels and tumour yield, whereas interstrain variation was less well predicted and may be determined by other susceptibility factors. Using the techniques of ^{32}P-postlabelling, immunoassay or mass spectrometry (MS) it is possible to detect DNA or protein damage (adducts) caused by genotoxic carcinogens in normal human tissues. In many cases the level of endogenously produced damage is comparable to, or greater than, that seen following exogenous exposures to carcinogens from for example occupational sources or tobacco smoking. Superior analytical methods are still required to improve the sensitivity of adduct detection for monitoring low level human exposures, and to identify the chemical nature of many of the DNA adducts, which is only indirectly achievable by the technique of ^{32}P-postlabelling. We have achieved greater selectivity and sensitivity of adduct detection in human tissues using accelerator MS (AMS), following for example administration of ^{14}C-tamoxifen (collaboration with K Turteltaub and R C Garner). We have also developed a ^{32}P-postlabelling method for the detection of phosphotriesters, which, because of their abundance and stability, may offer a further increase in sensitivity over standard postlabelling techniques for measuring adducts.

An Official Journal of the
Society of Toxicology
Supplement

38th ANNUAL MEETING

TOXICOLOGICAL SCIENCES

Formerly Fundamental and Applied Toxicology

The Toxicologist

Oxford University Press

Volume 48, Number 1-S, March 1999

The Toxicologist

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

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 38th Annual Meeting of the Society of Toxicology, held at the Ernest N. Morial Convention Center, New Orleans, Louisiana, March 14-18, 1999.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 419.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 444.

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

Copies of *The Toxicologist* are available at $45 each plus $5 postage and handling (U.S. funds) from:

Society of Toxicology
1767 Business Center Drive, Suite 302
Reston, VA 20190-5332
http://www.toxicology.org