a highly selective and characteristic pattern of neurological sequelae in laboratory animals. The specific neuronal target of artemisinin derivatives is unknown, and there exists an inability to predict artemisinin-induced neurotoxicity in advance of its occurrence. At WRAIR, we are utilizing an in vitro microarray-based approach to tackle these challenges. Total RNA was isolated from established rat neuronal cell lines and primary cell cultures exposed to fractional inhibitory concentrations of artemisinin derivatives, other neurotoxic antimalarials and neurotransmitters. Affymetrix U34 Rat Toxicology GeneChips were used to generate gene expression profiles at different time points for the different cell types after exposure to the drugs. Gene expression profiles were analyzed used GeneSpring and Partek data analysis suites, in order to identify transcripts significantly and selectively modulated by artemisinin toxicosis, describe general changes in transcriptional responses induced by artemisinin treatment, and assess the potential usefulness of Affymetrix U34 arrays as predictive toxicological tools. Results will be discussed in light of earlier studies addressing the mode of action of artemisinin compounds and their valuable role in malaria chemotherapy.

P4E8
New statistical methods for analyzing gene array data in toxicological studies

W.C. Griffith*, E.L. Faustman, J. Brutlag
Institute for Risk Analysis and Risk Communication, *Department of Environmental Health*, *University of Washington*, *Seattle*, *WA*, *USA*

New statistical methods are needed to evaluate the enormous volume of data being generated by gene microchip arrays to identify gene expression patterns altered by toxicological response to contaminant exposures. Potential applications of microarrays to toxicology and risk assessment include identifying gene-expression networks and toxicant-specific signatures that can be used to define mode of action and for exposure assessment. Many of the statistical issues for analyses of gene microchip array data still remain largely unexplored. The statistical techniques being described in the literature are primarily for classifying genes into groups using cluster analysis for those with similar patterns of expression (Eisen et al., Proc. Natl. Acad. Sci. 95:14863, 1998). Our approach has been to instead analyze gene expression profiles as a classification problem. We have developed statistical tools that will instead use groups of genes with a similar known function to identify other genes that have the most similar time or dose related patterns of expression. Preliminary examination has been made of gene microchip data available in internet libraries. These tools used a classification model and an EM algorithm implemented in BUGS (MRC Biostatistics Unit, Cambridge, UK, BUGS, Bayesian inference Using Gibbs Sampling web page http://www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml, May 2000). Application of these tools to this example data set indicates that this is a viable approach for sorting through patterns of gene expression of a large number of genes to provide toxicologists with a useful method to understand gene function.

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P4F
Methods

P4F1
Chemical identification of a toxicant leached from a surgical drain

P.D. Siegel*, G.J. Depree, E. Shriver, G.A. Knudsen, P.H. Nicolaysen, J. Meade
NIOSH, *Morgantown*, *WV*, *USA*

Residual chemicals can leach from medical devices that contact biological membranes. In repeat studies, when subcutaneously implanted into mice, one brand (Brand A) of latex surgical drain consistently produced acute toxic reactions resulting in mortality within 12 h. This was not found with other brands tested. This abstract describes the methodological approach used to isolate and identify the toxic agent leached from Brand A. Experiments were designed to selectively leach/partition the toxic substance from the surgical drain into latex compatible solvents, characterize the washes by GC/MS, and assess the toxicity of the washed drains. A non-toxic drain (Brand B) was used as a control. Methanol and acidic water, but not saline or alkaline water wash resulted in loss of toxicity from Brand A. This suggested that the toxic agent had some solubility in methanol and was probably a basic compound. Zinc diethyl dithiocarbamate (ZDEC) was the only compound found in both the methanol and acidic water Brand A washes, but not in the alkaline water wash nor any of the Brand B washes. Subcutaneous administration of ZDEC produced the same spectrum of toxic reactions as Brand A. The general approach of selective leaching/partitioning coupled to chemical analysis and toxicological assessment provides a useful tool for the identification of potentially hazardous residues in medical device materials.

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P4F2
Cytotoxicity of hypertonic sodium chloride solutions in a muscle irritation model in vitro

C.N. Edwards[1], O. Svendsen[2]*
[1] *Scantox A/S*, *Lille Skensved*, *Denmark*; [2] *Department of Pharmacology and Pathobiology*, *The Royal Veterinary and Agricultural University*, *Frederiksberg C*, *Denmark*

Intramuscular injection of hypertonic sodium chloride solutions (e.g. 5% NaCl) is known to be very painful to people and

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Abstracts

Lectures

Deichmann Lecture
Apoptosis and toxicology — What relevance?

D.L. Vaux
The Walter and Eliza Hall Institute of Medical Research, Royal Parade, Parkville, Vic., Australia

All cells are mortal — i.e. they can be killed if a vital metabolic process is blocked. All cells can engage in a variety of stress responses, such as the heat shock response, when vital processes are slowly, or only partially, inhibited. These stress responses involve detection of the damage, transduction of signals, and activation of a response, such as production of heat shock proteins, proteases, or chaperones. Many cells possess mechanisms whose purpose is to kill the cell. Such physiological cell death mechanisms are used to remove unwanted or damaged cells. Among metazoans, physiological cell death is implemented by a family of cysteine proteases, termed caspases, that exist in a latent state even in healthy cells. Cells killing themselves via activation of their caspases typically exhibit an appearance termed 'apoptosis'. Apoptosis is not only used to remove cells in physiological circumstances, such as during development, but is also a common response to cell stress. Thus many cells will detect damage to, or malfunctioning of, vital metabolic processes, and generate signals that lead to activation of the caspases, and apoptotic death of the cell. This has led to a great deal of confusion, because many drugs and toxins with known biochemical functions have been found to induce apoptosis, and rather than this being interpreted as a stress response, it has often wrongly been assumed that apoptosis is a direct effect of the drug or toxin.

Plenary Lectures

L1
The pathogenesis of prion diseases

S.J. DeArmond
Department of Pathology, University of California, San Francisco, CA, USA

Prion diseases occur because the full length prion protein (PrP) can exist in two conformations: (1) a normal conformation in which the N-terminal half of the molecule has little or no β-sheet, which is characteristic of PrPc; and (2) an abnormal, pathogenic conformation in which the N-terminal half acquires a β-sheet conformation, which is characteristic of PrPSc in scrapie and bovine spongiform encephalopathy (BSE) of animals and Creutzfeldt-Jakob disease (CJD) in humans. The property of the prion protein which gives prion diseases the characteristics of a slow virus infection is the efficient conversion of PrPC into nascent PrPSc when the former physically interacts with 'infecting' PrPSc. Sporadic CJD accounts for 85% of human prion diseases and appears to be initiated by the spontaneous conversion of PrPC to PrPSc (a one per million event). Familial CJD (15%) is caused by mutations of the PRNP gene. The PrPSc in sporadic and familial CJD is infectious. Prion strains are defined by the disease phenotype they produce in a host animal. Conformational dependent immunoassays indicate that the PrPSc comprising each prion strain has a different conformation, possibly as a result of different amounts of β-sheet and different PrPSc polymerization patterns. All of the parameters that define each prion strain can be modified by manipulating the amino acid sequence of PrP, which supports the protein only hypothesis. Finally, neuronal dysfunction and death in prion diseases require both the conversion of PrPC to PrPSc and the accumulation of nascent PrPSc in or on neurons and their processes.

L2
Food and cancer

T. Sugimura
National Cancer Center, Tokyo, Japan

Food is an important factor in determining cancer incidence in many countries and regions. Food components relevant to cancer development can be divided into macro- and microcomponents. The former tends to act indirectly. The latter usually has a clearly defined action, for example as genotoxic agents. Food can have both positive (carcinogenic) and nega-

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