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IMPLICATIONS FOR TOXICOLOGY, MEDICINE AND RISK ASSESSMENT

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ABSTRACT BOOK

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HORMESIS: ITS INTEGRATION INTO THE RISK ASSESSMENT PROCESS

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Hormesis has "come of age." Inverted dose-responses now commonly appear in journals of both basic and applied science. Clear evidence of growth in interest (and acceptance) is the dramatic increase in the numbers, breadth, and depth of peer–reviewed publications on the topic. On empirical evidence, alone, it seems unlikely that hormesis is either artifact or error. But, beyond compelling demonstrations, several highly-plausible hypotheses for modes of action promise both to expand and to focus new research. Notwithstanding overwhelming empirical evidence and testable hypotheses for mode of action, no consensus has emerged on the means to incorporate hormetic dose-responses into human health safety assessment. Progress on two fronts are likely to have the greatest influence on the future for incorporating hormesis into risk assessment. The first question goes to the basic elements of toxicology and risk assessment, in general. Two recent reports from the National Research Council (popularly known as "Toxicology in the 21st Century" and "Science and Decisions") predict vastly different futures. In a nutshell, the former foresees a totally novel approach to safety assessment (i.e., a combination of "omics" technologies and "pathway recognition") while the latter suggests that no such dramatic change lies ahead (rather, technical advancements to the *status quo*). The second question is an intersection of issues relating (1) to whether hormetic dose-responses can be generalized as either harmful, beneficial, both or neither, and; (2) to what constitutes an "adverse" effect (as distinguished from an "adaptive" effect). This talk is intended to initiate an ongoing dialog with the goal of focusing on the essential research agenda that can move hormesis from the status of an inconvenient truth to a useful tool.

DEFAULT LOW-DOSE LINEARITY FOR ALL ENDPOINTS? IMPLICATIONS FOR RISK ASSESSMENT AND RISK MANAGEMENT

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In the recent NAS report, *Science and Decisions*, and elsewhere, it has been suggested that, in the interests of harmonization, all endpoints, whether cancer or noncancer, should use linear low-dose extrapolation to evaluate potential health effects. I briefly review the scientific arguments for and against this proposal, but my focus is on what its adoption would mean to risk assessment and risk management from occupational, environmental, and consumer-product exposures. Invoking the principle does not allow measurement of the slope of the low-dose extrapolation line; the incremental slope would not be the same for everyone exposed, depending on biological variation among people as well as differences in their circumstances. Since every substance is toxic at high enough doses, it is implied that every decision to control one substance increases exposures (and hence risks) for others. Since the susceptibility of different people becomes challenged by such a shift, complex equity issues are raised, as some people's protection becomes others' induced disease. The logic of the linearity proposal that people in the tails of a population distribution of sensitivity are on the verge of responding (and so are susceptible to even small doses) leads to the expectation that shifts in that distribution will put more people into one tail and pull others out of the other tail, leading to an overall hormetic effect. I express my judgment that the logic behind universal low-dose linearity is flawed, but that if it is nonetheless accepted, a host of unintended risk management consequences follow, with every problem becoming a risk-risk tradeoff in which the competing risks cannot be measured.

HORMESIS IN REGULATORY RISK ASSESSMENT: SCIENCE AND SCIENCE POLICY

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Is the lack of consideration of hormesis in EPA regulatory risk assessment a matter of science or science policy? After a discussion of the process for developing risk assessment guidelines in EPA I will look at the ways in which the Agency has considered the scientific aspects of hormesis and its potential implications for risk assessment. Research funded by EPA has clearly evaluated, and found, evidence of hormesis in some settings. Almost 10 years ago the Agency gave considerable attention to hormesis and risk assessment in its annual *Issues and Applications in Toxicology and Risk Assessment conference*. At the same time, there has been considerable pushback from Federal scientists and others on the possibility of consideration of hormesis in regulatory risk assessment. Today, there is no mention of hormesis in any EPA science policy documents like the guidelines for cancer risk assessment, developmental toxicity risk assessment or neurotoxicity risk assessment. One can imagine two potential reasons for the lack of consideration of hormesis; either the science is considered incomplete or not applicable or science policy choice has been made to disregard the concept. In addition to concerns about hormesis science it seems likely that science policy considerations are playing a major role. For example, the Guidelines for Carcinogen Risk Assessment assert that EPA's job is to use risk assessment to set protective levels of exposure and, when confronted with uncertainty, "Agency policy…. should be health protective." At this point it would appear that the EPA does not believe that consideration of hormesis would be health protective.

There are clearly factors continuing to push the Agency toward consideration of hormesis. Both the National Research Council of the National Academy of Sciences and the EPA's Science Advisory Board have suggested that the Agency consider hormesis in specific instances. On the policy side, Cass Sunstein, the Administrator of the Office of Information and Regulatory Affairs within the Office of Management and Budget has, in his past scholarly writing, suggested that consideration of hormesis is important to sound public health decision-making.

There are still scientific hurdles for the use of hormesis in risk assessment. Hormesis science needs to address concerns including generalizability, different endpoints for beneficial and adverse responses, and quantitative prediction of the boundary between hormetic and adverse effects. Yet, given the EPA's science policy position, it seems that consideration of hormesis is unlikely to change until clear evidence emerges that <u>not</u> considering hormesis is public health threat. The evolution of science policy to specific decision contexts, as suggested in the recent NAS/NRC report *Science and Decisions*, would require weighing of competing risks. Risk assessment in a decision context, rather than in isolation, might force consideration of the potential public health implications of inappropriate risk estimates and further discussions of whether consideration of potential hormetic effects is actually health protective. In short, hormesis awaits evolution in both science and science policy.

NO GENOTOXIC CONSEQUENCES OF DAILY DOSES OF EMS INDUCING UP TO 380'000 DNA-ALKYLATIONS/CELL/DAY
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GENERIC HOCKEY-STICK MODEL FOR UNBIASED BENCHMARK-DOSE AND NET-POTENCY ESTIMATION
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THE ALCOHOL AND NPC META-ANALYSIS IN THE CONTEXT OF OTHER DOSE-RESPONSE RELATIONSHIPS VS. ALCOHOL AND OTHER OUTCOMES
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AGRICULTURE, INSECTS AND HORMESIS: EVIDENCE AND CONSIDERATIONS FOR STUDY
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EXPOSURE TO NANOPARTICLES AND HORMESIS
Ivo Iavicoli, Catholic University of Sacred Heart, Roma, Italy
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A NOVEL MODEL FOR THE CYTOTOXICITY OF INSOLUBLE METALLIC NANOPARTICLES
Bobby R. Scott, Lovelace Respiratory Research Institute, Albuquerque, NM

A NEW PLATFORM TECHNOLOGY FOR THE SELF-ASSEMBLY OF 3D LIVING MICROTISSUES
Jeffrey R. Morgan, Brown University, Providence, RI

NO GENOTOXIC CONSEQUENCES OF DAILY DOSES OF EMS INDUCING UP TO 380'000 DNA-ALKYLATIONS/CELL/DAY

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The accidental contamination of an HIV medication with EMS (Ethyl Methansulfonate) triggered non-clinical studies into the (geno)toxicity of this the well known mutagen/ carcinogen/ teratogen. The studies were performed to provide reassurance to the patients that their exposure to EMS did not carry an increased risk for adverse effects. The complete investigations are published in a special issue of Toxicology Letters (Vol 190, No 3). Here we focus on the shape of the dose response curves of in vivo genotoxicity (micronucleus test for chromosomal damage, Muta^{TM}Mouse test for lacZ gene mutations). Mice were treated with repeated doses with EMS ranging from 1.25 to 260 mg/kg/day. As reference genotoxin we included a second ethylating agent, ENU (Ethyl Nitrosourea) at doses between 1.1 and 22 mg/kg/day. ENU is known to be more effective than EMS in ethylating DNA at oxygen sites.

As expected, both, EMS and ENU induced clear increases of mutagenic effects. However, for EMS the dose response relations were distinctly non-linear. Doses up to 25 mg/kg did not induce mutations in bone marrow and GI tract, and doses up to 50 mg/kg did not induce mutations in the liver. Micronuclei were not induced at doses up to 80 mg/kg/day. The thresholds were affirmed by statistical analysis. Further, the statistical assessment indicated a significantly negative slope of the dose response curve for induction of micronuclei at low doses. In contrast to EMS, our studies could not provide evidence for a thresholded dose response for ENU. But data were compatible with a hypothesized threshold of ca 0.3 mg/kg/day.

Our concomitant pharmacokinetic investigations allowed us to estimate the number of DNA alkylations induced by EMS at the threshold doses. We could conclude that about 380’000 DNA alkylations were induced in each liver cell at each daily dose of 50 mg/kg without any increase of the mutation frequency.

GENERIC HOCKEY-STICK MODEL FOR UNBIASED BENCHMARK-DOSE AND NET-POTENCY ESTIMATION

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Now widely applied as a routine component of regulatory toxicity and cancer risk assessment, USEPA Benchmark Dose Model software (BMDS) and related procedures comprise a suite of dose-response models, none of which (in routinely applied default configurations) reflect the possibility of hormesis or induced risk reduction. Not only does the number of models in the BMDS suite continue to grow, the quasi-statistical, decision-tree approach used to implement them continues to increase in complexity, without any assurance concerning overall error rates associated with multiple model fits and multiple hypothesis tests involved. An alternative, single, more easily applied Generic Hockey-Stick (GHS) model is proposed to better achieve all BMDS goals, in a way that objectively addresses the possibility of negative or net-negative dose-response trend at low doses. The relative performance of GHS vs. BMDS estimators of benchmark dose and of potency was characterized using different sets of simulated data based on different corresponding underlying assumptions concerning true dose-response. Ability of the GHS model to objectively characterize low-dose trends in response and estimated risk is illustrated by an application to rodent bioassay data for a genotoxic environmental chemical observed to reduce tumor risk.

AGRICULTURE, INSECTS AND HORMESIS: EVIDENCE AND CONSIDERATIONS FOR STUDY

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Insects are ubiquitous, crucial components of essentially all terrestrial and fresh-water ecosystems. In agricultural settings especially, they are also subjected to – either intentionally or unintentionally – a wide array of synthetic pesticides and other chemical stressors. These ecological underpinnings, the amenability of insects to laboratory and field experiments, and our strong knowledgebase in pesticide toxicology, make the insect-insecticide model an excellent one to study many questions surrounding hormesis. Nevertheless, barring the use of *Drosophila* as a model in biomedical-type investigations, insects have been underutilized when examining the phenomenon. Where hormesis hypotheses have been tested using insects and chemical stressors, results clearly demonstrate stimulatory effects for multiple taxa as measured through several biological endpoints, both at individual and population levels. Relevant investigations to date, however, have been relatively limited in scope, and although such an approach is invaluable, many questions are outstanding given the myriad of responses, chemical and biological transformations, and ecological interactions that are likely to occur in the field. This paper considers directions for future study of insect hormesis while reviewing factors that are likely to challenge researchers in the move to more mechanistic- and field-based investigations, particularly as they relate to numerous questions in insect pest management and insect ecology.

EXPOSURE TO NANOPARTICLES AND HORMESIS

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Nanoparticles (NPs) are routinely defined as particles with sizes between about 1 and 100 nm. They are increasingly being manufactured and used for commercial purpose because of their novel and unique physicochemical properties. Given that human exposure to these particles is inevitable, there is an increasing demand for additional toxicological research. Currently, there are uncertainties in key factors that influence health risks such as: routes of exposure, distribution, accumulation, excretion and dose-response relationship following exposure to NPs. In particular, there is considerable uncertainty with regard to the nature of the dose-response at low levels of exposure, (*i.e.*, below the toxic threshold). In fact, some studies have shown that NPs display a biphasic, or hormetic dose-response. For example, human alveolar epithelial cells exposed for 24 h to various concentrations of CNTs (5, 10, 50 and 100 μg/ml), showed a stimulation of reactive oxygen species (ROS) production at 5 and 10 μg/ml, while the ROS levels decreased at 50 and 100 μg/ml. Neurite outgrowth in murine neuroblastoma cells treated with 25 and 50 nM of thioglycolic acid (TGA)-capped cadmium telluride gelatine-quantum dots also demonstrated a hormetic dose-response. Specifically, exposure to the 25 nM concentration led to a slight increase in total neurite length. In contrast, cells exposed to the 50 nM concentration showed a significant reduction of viability, and a moderate level of neurite outgrowth. Titanium dioxide (TiO_2) NPs have also been shown to enhance feeding rate, food assimilation, and catalase activity a single-species laboratory test with terrestrial invertebrates (*P. scaber*). In addition to the hormetic response of the murine cell line, human cell lines, and the *in vivo* (invertebrate) model reviewed here, we will present an analysis of hormetic dose-responses that have been observed for various NPs described in the literature.

A NOVEL MODEL FOR THE CYTOTOXICITY OF INSOLUBLE METALLIC NANOPARTICLES

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This presentation introduces a novel microdosimetric model for **me**tallic-**na**nomaterial-**p**articles (MENAP)-induced cytotoxicity. The focus is on the cytotoxicity of engineered insoluble MENAP which are used in new products for consumers, industry, and medicine. The small size of engineered MENAP facilitates their uptake into cells and transcytosis across epithelial and endothelial cells into the blood and lymph circulation. Translocation over the nervous system via axons and dendrites of neurons is an important mode of transport. In addition, the mitochondria and the nucleus have been identified as key targets for uptake (called hits) of MENAP. Thus, there is concern about potential health effects from long-term exposure to these nanoparticles. Potential effects include neurological diseases, cardiovascular diseases, and cancer. Dose-response models for MENAP-induced cellular effects provide an important first step towards developing needed quantitative models for assessing health risks from MENAP exposure. The ***s**tochastic **t**hreshold **m**icrodose (STM) model* to be presented introduces novel stochastic microdose metrics for use in constructing dose-response relationships for the frequency of specific stochastic cellular (e.g., cell killing) or subcellular (e.g., mitochondria dysfunction) effects. The metrics include the exposure-time-dependent, *specific mitochondrion burden*, the *specific nuclear burden*, and their respective expectation values (i.e., averages) called the *mitochondria burden* and *nuclear burden*. The STM model incorporates a stochastic threshold specific mitochondrion burden, N_m, of MENAP for triggering the autophagic-mode death and a separate stochastic threshold specific nuclear burden, N_n, for triggering the apoptotic-mode of death. The model has been used to characterize the in vitro cytotoxicity of 80-nm copper nanoparticles to rat somatosensory neurons. Evidence was obtained for the existence of a hypersensitive subpopulation of neurons that appears to be completely destroyed when the mitochondria burden (an average) exceeds about 6 copper particles per each mitochondrion. Health risk implications for use of copper nanoparticles in skin creams and sprays will be discussed.

A NEW PLATFORM TECHNOLOGY FOR THE SELF-ASSEMBLY OF 3D LIVING MICROTISSUES

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The Petri dish, a technology that is over 100 years old, is widely used throughout the world, but there is growing recognition that cells grown as a thin single layer on a flat plastic dish do not adequately mimic the function, nor the geometry of natural tissues and organs. We have devised a new and versatile platform technology for growing cells in three dimensional (3D) aggregates which form the natural cell-to-cell interactions that occur *in vivo*. We use computer aided design (CAD), rapid prototyping and replica molding to design and fabricate micro-molded hydrogels (agarose) that are nonadhesive for cells and that direct the self assembly of the cells into 3D living microtissues. When mono-dispersed cells are seeded onto the surface of our micro-molded nonadhesive hydrogel, they settle into the small recesses, are unable to attach to the nonadhesive surface and so cell-to-cell adhesion drives the self assembly of a 3D multi-cellular microtissue. Microtissue size is uniform and is controlled by the number of cells seeded. Microtissues with two or more different cell types that replicate heterotypic cell-to-cell interactions of *in vivo* tissue units can be produced by mixing cell types prior to seeding. Microtissue shape is controlled by the geometry of the micro-mold, so it's possible to produce microtissues that replicate *in vivo* 3D architectures. A single pipetting step can create *in vitro* hundreds to thousands of uniform living 3D microtissues that are significantly closer in size, shape and cellular function to *in vivo* tissues and organs than cells grown on flat plastic Petri dishes. Like the 100 hundred year old Petri dish, this new technology has widespread applications in tissue engineering, stem cells, cancer biology, drug discovery, toxicology and an understanding of the dose response.

BIOMEDICAL SESSION

LOW-DOSE CARDIOTONIC STEROIDS INCREASE SODIUM-POTASSIUM ATPASE ACTIVITY AND PREVENT HIPPOCAMPAL NEURONAL LOSS FROM EXPERIMENTAL ISCHEMIA
Peter Bergold, SUNY-Downstate Medical Center, Brooklyn, NY
Martin Oselkin, SUNY-Downstate Medical Center, Brooklyn, NY
Dezhi Tian, SUNY-Downstate Medical Center, Brooklyn, NY

METHAMPHETAMINE PRECONDITIONING CAUSES CHANGES IN STRIATAL TRANSCRIPTIONAL RESPONSES TO LARGE DOSES OF THE DRUG
Jean Lud Cadet, Christie Brannock, Bruce Ladenheim, Michael T. McCoy, and Irina N. Krasnova, Molecular Neuropsychiatry Research Branch, DHHS/NIH/NIDA Baltimore, MD

BRAIN ADAPTATION AND HORMESIS
Jun Chen, Uniformed Services University of the Health Sciences, Bethesda, MD
Robert H. Lipsky, Inova Fairfax Hospital, Falls Church, VA
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Antonello Novelli, University of Oviedo, Oviedo, Spain
Ann Marini, Uniformed Services University of Health Sciences, Bethesda, MD

COGNITIVE ACTIVATION BY DEEP BRAIN STIMULATION: THE YERKES-DODSON LAW REVISITED
Ronald Mair, University of New Hampshire, Durham, NH

CORTISOL EXHIBITS BI-DIRECTIONAL CONTROL OF HUMAN INFLAMMATORY RESPONSES *IN VIVO*
Mark P. Yeager, Dartmouth-Hitchcock Medical Center, Lebanon, NH
Patricia A. Pioli, Dartmouth Medical School, Hanover, NH
Paul M. Guyre, Dartmouth Medical School, Hanover, NH

U-SHAPED DOSE RESPONSES AND ANTITUMOR ACTIVITY
Kashi Javaherian, Harvard Medical School, and Tufts University School of Medicine, Boston, MA

HORMETIC RESPONSE TO LIFELONG MITOCHONDRIAL OXIDATIVE STRESS
Sano Motoaki, Keio University School of Medicine, Tokyo, Japan

HORMESIS AND EXERCISE: SUPPORT FOR AN INVERTED-U RESPONSE TO ACUTE AND CHRONIC WORK
Bradley D. Hatfield, University of Maryland, College Park, MD

THE USE OF MODIFIED STREPTOLYSIN O TO INDUCE ACCELERATED WOUND HEALING AND CONNECTIVE TISSUE REPAIR

Volken M. Gurel, Beech Tree Labs, Inc., Providence, RI
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LOW-DOSE CARDIOTONIC STEROIDS INCREASE SODIUM-POTASSIUM ATPASE ACTIVITY AND PREVENT HIPPOCAMPAL NEURONAL LOSS FROM EXPERIMENTAL ISCHEMIA

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The sodium-potassium ATPase (Na/K ATPase) is a major ionic transporter in the brain and is responsible for the maintenance of the Na+ and K+ gradients across the cell membrane. Cardiotonic steroids such as ouabain, digoxin and marinobufagenin are well-characterized inhibitors of the Na/K ATPase. Recently, cardiotonic steroids have been shown to have additional effects at concentrations below their IC50 for pumping. The cardiotonic steroids ouabain, digoxin, and marinobufagenin all show an inverted U-shaped dose-response curve with inhibition of pumping at concentrations near their IC50, while increasing Na/K ATPase activity at doses below their IC50. This stimulatory effect of cardiotonic steroids was observed in vitro in hippocampal slice cultures as well as in the hippocampus in vivo. Increased Na/K ATPase activity has been shown to protect slice culture neurons from hypoxia-hypoglycemia. Ouabain protected slice culture neurons from experimental ischemia at concentrations that increased Na/K ATPase. This protective effect was observed when ouabain was dosed 30 minutes before, or 2 hours following experimental ischemia. Ouabain no longer protected against experimental ischemia if the increase of Na/K ATPase was blocked. These data suggest that the protective effect of ouabain was due to increased Na/K ATPase activity. The demonstration of a neuroprotective effect of cardiotonic steroids could potentially assist in the treatment of stroke since digoxin, one of the cardiotonic steroids examined in this study, has approval by the Food and Drug Administration and can be safely administered at the concentrations that increase Na/K ATPase activity.

METHAMPHETAMINE PRECONDITIONING CAUSES CHANGES IN STRIATAL TRANSCRIPTIONAL RESPONSES TO LARGE DOSES OF THE DRUG

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Methamphetamine (METH) is an illicit drug which is neurotoxic. Administration of moderate to large doses of drug causes marked decreases in dopamine levels in the brains of animals. In contrast, repeated injections of small nontoxic doses of the drug followed by a challenge with toxic METH doses provide protection against monoamine depletion. The present study tested the possibility that repeated injections of relatively small doses of the drug could reprogram the transcriptional changes to larger METH doses. We found that METH preconditioning did provide significant protection against METH-induced striatal dopamine depletion. In addition, the presence and absence of METH preconditioning were associated with substantial differences in the identity of the genes affected by METH in the rat striatum. These genes include trophic factors such brain derived neurotrophic factor (BDNF) and VGF, AP1 transcription factors, Heat shock protein 27, some members of the Bcl-2 family of death related proteins, and some genes that encode antioxidant proteins including copper/zinc superoxide dismutase (CuZnSOD) and heme oxygenase-1. Our observations indicate that, similar to other models of preconditioning, METH preconditioning is associated with reprogramming of changes in the brain transcriptome that occur after injurious insults. Future investigations using the METH preconditioning model should provide greater insight into drug-induced neuroadaptations in humans exposed to psychostimulants.

BRAIN ADAPTATION AND HORMESIS

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Organisms have to adapt to even small environmental changes if they are to survive. The brain adapts through mechanisms referred to as plasticity. Adaptation plays a key role in allowing the brain to process experiences dictated by the environment and change accordingly. Plasticity, collective mechanisms that oversee the ability of the brain to modulate in response to changes in the environment, mediates cognition. Plasticity allows the brain to process information from the environment rapidly and with exact precision. Plastic responses are mediated via synapses in the brain. Synaptic function is crucial for the organism to respond rapidly to experience over the lifetime of the organism. These experience-driven functional alterations require receptors, signal transduction pathways, transcription and translational mechanisms to respond rapidly. Neurons in different brain regions are connected via synapses. Plastic responses communicated through the rapid firing of neurons which underlies the organism's ability to perceive, calculate, plan, remember, and learn. Glutamate is the major excitatory neurotransmitter in brain. Activation of the N-methyl-D-aspartate receptor (NMDA) mediates plastic responses in brain, producing a heretic effect at low concentrations of NMDA. Using both in vitro and in vivo experimental approaches, we will present data supporting the role of a major hormetic mechanism in neurons that requires brain-derived neurotrophic factor (BDNF), a major neuroprotective protein in brain. Low concentrations of NMDA, palytoxin or domoic acid does not affect neuronal survival. However, addition of low concentrations of palytoxin and domoic acid together are toxic to neurons. Because the brain has evolved to respond rapidly to environmental cues, exposure of neurons to subtle environmental changes can result in synaptic dysfunction and neuronal cell death. Thus, hormesis may play a crucial role in determining the outcome of synaptic function and may contribute to neurodegenerative disorders.

COGNITIVE ACTIVATION BY DEEP BRAIN STIMULATION: THE YERKES-DODSON LAW REVISITED

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The midline-intralaminar complex in central thalamus regulates forebrain arousal, influencing activity in distributed neural networks that give rise to organized cognitive and behavioral function during alert, wakeful states. These neurons receive arousal-related inputs from a number of sources, including the deep mesencephalic reticular nucleus; brainstem noradrenergic, serotonergic, and cholinergic nuclei; and histaminergic and orexinergic neurons in hypothalamus. Lesion studies have implicated the midline-intralaminar nuclei in working memory and related cognitive functions. Drug microinjection studies have confirmed these findings and provided evidence on an inverted-U shaped relationship between central thalamic activity and cognitive function. Drugs decreasing activity, through actions on $GABA_A$ or nicotinic cholinergic receptors, have revealed impairments that increase with dose. By contrast drugs that enhance activity by decreasing GABAergic tone or stimulating nicotinic or orexinergic receptors enhance measures of cognitive function up to an optimal level, above which performance declines. This inverted-U relationship has been confirmed by electrical deep brain stimulation (DBS). DBS provides a means to activate neurons momentarily and thus to study the influence of activation during different phases of memory function. DBS of the rostral intralaminar nuclei has revealed enhanced delayed matching performance with low stimulating currents and impairment at higher currents. These effects are observed when DBS is applied during the memory delay (retention) or choice response (retrieval) but not earlier during the sample phase (acquisition) of delayed matching trials, even when delays were short and the time between sample and choice responses minimal. The inverted-U relationship observed with microinjected drugs and DBS is consistent with the Yerkes-Dodson law, which describes an inverted-U relationship between arousal and behavioral performance. Alternatively these results may reflect desensitization associated with higher levels of stimulation, spread of drugs or current to adjacent structures, or activation of less sensitive neurons or receptors at higher DBS currents or drug doses.

CORTISOL EXHIBITS BI-DIRECTIONAL CONTROL OF HUMAN INFLAMMATORY RESPONSES *IN VIVO*

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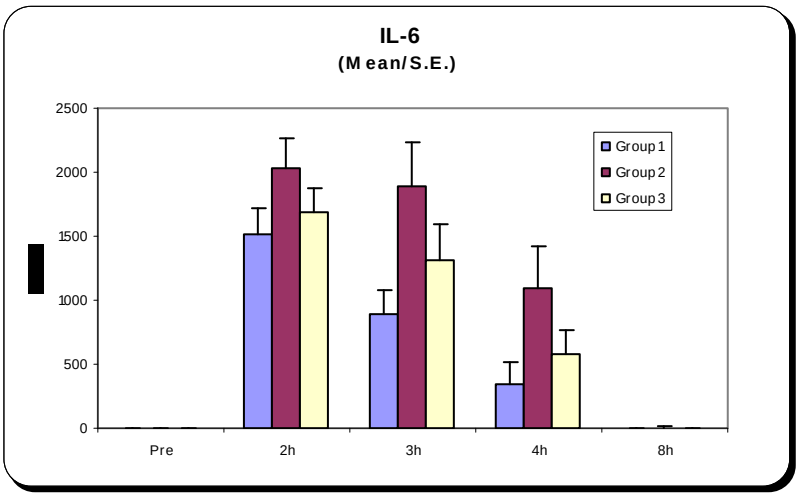
Cortisol is the natural glucocorticoid (GC) mediator of the human hypothalamic-pituitary-adrenal axis. Both natural and synthetic GCs have long been known to suppress inflammation and immunity. The striking anti-inflammatory properties of GCs are dose-dependent and more prominent at higher GC concentrations and/or with the use of more potent synthetic GCs. For this reason, virtually all GC research has examined the anti-inflammatory effects of sustained high concentrations of GCs. Recently, investigators have discovered a far more complex relationship between GCs and inflammation. When inflammatory effector cells are exposed to GCs in physiologic concentrations and for shorter periods of time (hours instead of days), they frequently enhance inflammatory immune process, particularly those of the innate immune system. In fact, when examined in detail, a bi-phasic dose relationship between GC concentration and inflammatory responses has frequently been noted. There are limited, but emerging data in humans to support this relationship. We recently randomized 36 healthy human volunteers to receive 1 of 3 pre-treatment exposures to intravenous cortisol over 6 hours from 0900-1500h: 1) saline control, 2) 1.5 ug/kg/min cortisol ('physiologic' cortisol), or 3) 3.0 ug/kg/min ('pharmacologic' cortisol). The following day (18 hours after cortisol exposure), participants received an intravenous injection of bacterial lipopolysaccharide (LPS) to induce a transient systemic inflammatory response. Over the next 8 hours, participants who received the physiologic, but not the pharmacologic dose of cortisol manifested a significantly increased inflammatory response (plasma interleukin-6 [IL-6]) to the LPS (Figure 1) compared to controls. This response was associated with a significantly decreased anti-inflammatory IL-10 response. The difference in cytokine responses was not due to adrenal suppression since cortisol concentrations were the same in all 3 groups after LPS. These data provide strong support for research to re-examine the generally accepted uni-dimensional relationship between GCs and inflammation. Instead of a simple dose-response relationship that equates more GC with greater suppression of inflammation, a bi-phasic or bell-shaped curve may better explain the relationship between GCs and inflammation.

Figure 1. Plasma IL-6 concentrations before and for 8 hours after exposure of healthy human subjects to intravenous LPS.



U-SHAPED DOSE RESPONSES AND ANTITUMOR ACTIVITY

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In 1971, Judah Folkman proposed the concept of angiogenesis (formation of blood vessels) as a major regulator of cancer. More than two decades later, two endogenous angiogenesis inhibitors called angiostatin and endostatin were discovered in his laboratory. We have been investigating the mechanism of these two antitumor proteins.

Studying antiangiogenic effects of the proteins in tumor-bearing mice demonstrated a nonlinear relationship between the volume of the tumor and the concentration of the administered recombinant protein. The results were U-shaped curves representing the biphasic characteristic of the tumor volume as a function of protein concentration. Both angiostatin and endostatin appear to share such properties. These results may have major implications towards understanding the mechanism of these two inhibitors.

Recently, we have found out that oligomeric state of endostatin plays an important role in relationship of its binding to the extracellularmatrix (ECM). A detailed binding study is in progress to shed light on the U-shaped behavior of the two proteins.

HORMETIC RESPONSE TO LIFELONG MITOCHONDRIAL OXIDATIVE STRESS

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Advanced age is one of the major independent predictor for poor outcome in patients with ischemic heart diseases. The aged myocardium displays a higher vulnerability to ischemic insults with a reduced ability to recovery. Despite advances in therapeutic strategies, cardiovascular disease remains the leading cause of death in elderly. We need to develop the new strategy aimed at protecting the senescence heart. Low levels of stressors interact with signaling systems that result in stress resistance, whereas high doses cause overt toxicity. “Hormesis” is the term for favorable biological responses to low levels of stressors. It should counteract a decline of the heart function with age and confer resistant to lethal levels of stressors. Mitochondria oxidative stress plays a key role in cardiac senescence. However it remains unknown how heart adapts to lifelong mitochondrial oxidative stress. We recently discovered that the heart has an intrinsic capacity to change the intracellular metabolism to counteract lifelong mitochondrial oxidative damage. Aldehyde, a major end-product of lipid peroxidation, acts a second messenger to trigger phosphorylation of eukaryotic translation initiation factor (eIF) 2α. Subsequent translational activation of activating transcription factor (ATF)4 up-regulates the gene expression of enzymes involved in amino acid biosynthesis and transport that ultimately provide precursor amino acids for glutathione biosynthesis, thereby increasing intracellular glutathione levels. Enhanced supply of NADPH via the pentose phosphate pathway concomitantly helps in the recycling of oxidized glutathione. As a consequence, heart with lifelong mitochondrial oxidative stress exhibited improved tolerance to ischemia-reperfusion injury. Our results indicate that mimetic triggers of hormesis may be a promising approach for the cardioprotection in the elderly.

HORMESIS AND EXERCISE: SUPPORT FOR AN INVERTED-U RESPONSE TO ACUTE AND CHRONIC WORK

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Physical activity is a stimulus to which the psychological and physiological responses and adaptations are shaped by intensity and volume of work. Consequences are also determined by individual differences such as age and genotype. The presentation will overview psychological responses to exercise underlying affective responses or 'feel better' effect. The impact of varying exercise intensities on cerebral cortical activity and self-reported mood will be offered as a process that determines long- term adherence. The long-term dose-response relationship between exercise and neurocognitive processes will be overviewed with particular emphasis on populations at genetic risk for dementia and Alzheimer's disease (AD). Our work suggests a protective effect of exercise on specific cognitive processes in both young (18 – 25 years) and older (50 – 70 years) cognitively intact carriers of the APOE e4 allele, an established risk factor for AD. The evidence has been observed at varying levels of measurement including behavioral, magnetoencephalographic (MEG), electroencephalographic (EEG), and neuroimaging (fMRI). Generally, carriers of APOE e4 derive cognitive benefit from exercise with increasing levels of engagement, while such a dose-response relationship is less apparent in non-carriers, who are at lower risk of dementia. In addition, there is task specificity for benefit with executive and memory-related performance showing greater benefit than that observed in response to other types of tasks. Finally, the presentation will discuss some recent work from our lab on the examination of the relationship between long-term patterns of exercise and telomere length in older men and women (50-70 years). As such, the study examined the relationship between dose of exercise and a marker of biological aging. The results suggest that moderate exercise provides a protective effect on telomere length compared to both low and high exercise energy expenditure levels thus suggesting an inverted-U relationship regarding the dose-response relationship for the benefit of exercise.

ML-05 (DETOXIFIED STREPTOLYSIN O): EFFECTS ON EXTRACELLULAR MATRIX AND IMMUNE RESPONSE GENE EXPRESSION IN PATHWAY-FOCUSED DNA MICROARRAYS

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ML-05 is a non-hemolytic form of streptolysin O, the membrane-damaging extracellular toxin produced by groups A, C, and G streptococci. This laboratory has previously demonstrated that ML-05 stimulates keratinocyte migration and proliferation in wound-healing scratch assays, and promotes wound healing in a human skin organ culture wound model. In the present investigations, pathway-focused DNA microarrays (Oligo GEArray system, SABiosciences) were used to elucidate the mechanism of action of ML-05 in wound healing processes. Normal human epidermal keratinocytes (NHEK), human dermal fibroblasts (HDF) and peripheral blood mononuclear cells (PBMC) were treated with varying concentrations of ML-05 (0.00002-200 IU/ml) for 24 hours, followed by RNA extraction and cRNA production. Samples were screened using arrays containing nucleic acid probes for 100 extracellular matrix genes (ECM) or 400 autoimmune and inflammatory response genes to profile gene expression. ML-05 upregulated two ECM genes, VCAN and CD44, that are directly related to keratinocyte migration and proliferation. Both the VCAN and CD44 gene products (versican and hyaluronan receptor, respectively) interact with hyaluronan in maintaining the structural and functional integrity of the ECM. Other upregulated ECM genes of interest that are known to be involved in wound healing processes included CTGF, which encodes connective tissue growth factor, and ICAM1, which encodes an intercellular adhesion molecule. ECM1, which encodes extracellular matrix protein 1, was upregulated in fibroblasts. ML-05 treatment also resulted in downregulation of several ECM genes, including MMP2 and MMP9 (matrix metalloproteinases 2 and 9), SPP1 (osteopontin), SPARC (osteonectin) and SPOCK1 (testican). ML-05 regulated the expression of a number of cytokine and chemokine genes. These results provide insight into the mechanisms through which ML-05 can stimulate wound healing with diminished scarring.

Radiation Session

Epidemiological Evidence for Possible Radiation Hormesis from Radon Exposure: A Case-Control Study Conducted in Worcester, MA
Richard Thompson, Johns Hopkins University, Baltimore, MD

Radiation-Induced Non Targeted Effects of Low Doses – What, Why and How?
Carmel Mothersill, McMasters University, Hamilton, Ontario, Canada
Colin Seymor, McMasters University, Hamilton, Ontario, Canada

Radiation Hormesis and Policy Considerations
Colin Seymor, McMasters University, Hamilton, Ontario, Canada
Carmel Mothersill, McMasters University, Hamilton, Ontario, Canada

Why CT Scans are Like Exercise and Can Reduce Cancer Risk
Douglas Boreham, McMasters University, Hamilton, Ontario, Canada
Nghi Phan, McMasters University, Hamilton, Ontario, Canada
Mike DeLisio, McMasters University, Hamilton, Ontario, Canada
Gianni Parise, McMasters University, Hamilton, Ontario, Canada

New Evidence for the Prevention of Diabetes and its Complications by LDR: Potential Clinical Application
Lu Cai, University of Louisville, Louisville, KY

EPIDEMIOLOGICAL EVIDENCE FOR POSSIBLE RADIATION HORMESIS FROM RADON EXPOSURE: A CASE-CONTROL STUDY CONDUCTED IN WORCESTER, MA

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Data from a case-control study of lung cancer and residential radon exposure conducted in Worcester County, MA, will be presented. A total of 200 cases and 397 age and gender-matched controls from a single HMO were recruited for the study. Emphasis was placed on accurate and extensive, year-long radon dosimetry with etch-track detectors and careful questioning about historic patterns of in-home mobility. In addition, an extensive profile of demographic characteristics, smoking patterns, and years of occupational exposure was obtained for all subjects. Risk of lung cancer from radon exposure was estimated by conditional logistic regression models that controlled for the above listed demographic, smoking, and occupational covariates. Preliminary exploratory analyses revealed a non-linear association between exposure and cancer risk. Radon exposure modeled with a linear spline term at the optimally determined knot of 69 Bq m^{-3} gave a statistically significant adjusted odds ratio (AOR) [95% CI] per Bq m^{-3} = 0.98 [0.970, 0.998]. This result demonstrates a negative risk in this exposure region that is consistent with those reported elsewhere that modeled radon exposure with cubic spline terms as well as with categories of exposure (Thompson, RE et al 2008). In contrast, the estimated risk for cancer above 69 Bq m^{-3} was found to be positive (AOR [95% CI] per 100 Bq m^{-3} = 1.24 [0.88, 1.77]). Although non-significant, this estimated AOR is comparable to that reported in the larger North American pooling study for subjects with ≤ 2 residences and ≥ 20 years with α-track air monitors (AOR [95% CI] per 100 Bq m^{-3} = 1.18 [1.02, 1.43], Krewski, D et al 2006). Further investigation of results from case-control studies conducted at other geographical sites that either support or contradict the non-linear dose-response relationship between lung cancer and radon found in the Worcester data will also be considered.

RADIATION-INDUCED NON TARGETED EFFECTS OF LOW DOSES – WHAT, WHY AND HOW?

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Ever since the grudging acceptance that non-targeted effects (NTE) can be measured in unirradiated cells or distant progeny of irradiated cells, the discussion has raged about the relevance of these effects. For the purposes of this presentation, NTE are defined as effects not associated with DNA lesions due to energy deposition in the cell showing the effect and so include genomic instability and bystander effects. Obviously, it is important to consider relevance for practical applications such as radiation protection and radiotherapy. To this end this paper will review data from in vivo experiments, which address questions about risk after medical and environmental exposures. However a major area of interest is the intrinsic relevance of these mechanisms in biology. Arguments will be made in this paper, that non-targeted effects (NTE) may call into question not only radiation effects paradigms such as the linear-non-threshold model (LNT), but may also have relevance to wider mechanisms in cancer biology, population ecology and evolutionary biology concerning process of selection, the transmission of heritable traits, the relevance of "social" interactions between cells, organisms and populations and the mechanism by which cells/organisms respond rapidly to environmental stress. This paper will also argue that a key consequence of findings in NTE biology is that at any given level of organization, from gene to ecosystem – communication of stress signals and heritability of stress adaptations provide the bridges linking one hierarchical level to the next and enable the rapid propagation of change triggered by stress at one level, resulting in change at a higher (or lower?) level. This addresses a major problem in evolutionary biology because while the molecular mechanisms of natural selection are fairly well understood a major knowledge gap exists in translating mutational drift at the level of the individual cell to natural selection at the ecological level where sociobiological factors are so important. The existence of the mechanism discovered in the NTE field provides a glimpse of a major way that evolution could be regulated through communicated signals between cells, individuals, and populations, These control and optimize responses at the level of the population and coordinate the emergence of exquisitely tuned systems which can adapt rapidly to micro or macro environmental change. It is likely that consideration of these mechanisms could also be of benefit in cancer biology providing new insights into the regulation of cancer cell social groups and how these interact with the host.

RADIATION HORMESIS AND POLICY CONSIDERATIONS

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As human beings we tend to care more for close friends and family than other unfamiliar members of our species. Although this contravenes many ethical rules (including the so-called "golden rule") it can be accommodated under a form of pragmatic ethics. Politicians generally understand pragmatic better than ethics, and tend to think of effects in terms of "How would you feel if it were your aunt?" (Or how can I sell this to the electorate?) By thinking in terms of smaller groups, any decisions tend to become individuated, so that, for example, a cancer in one person is seen as a problem for the species. This, when combined with concepts such as the "precautionary principle" mean that in pragmatic terms it is justifiable to use a model accepted to be wrong (such as LNT) provided it does not harm any individual. If it could be proven that this policy were harming individuals, the policy would have to be changed.

Other policy considerations occur in environmental areas, where individuation does not occur, and effects are monitored at the population level.

This paper will attempt to address the discrepancies between the two approaches, and assess how other issues such as economic considerations and public perception also impact on policy considerations.

WHY CT SCANS ARE LIKE EXERCISE AND CAN REDUCE CANCER RISK

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Low dose ionizing radiation from diagnostic X-rays during CT scans produces reactive oxygen species (ROS) that are known to up-regulate anti-oxidant processes and induce protective adaptive responses. These same ROS are induced by oxidative metabolism during physical exercise. Therefore, we compared adaptive responses in mice following exposure to repeated low dose CT scan X-rays and/or exercise. Our research has shown that repeated CT scans, exercise, or both combined can adapt cells and protect them from the effects of high dose ionizing radiation. When CT scans and exercise are combined, the adaptive effects appear to be additive or synergistic. DNA damaged was assessed using the gammaH2AX foci assay or the mirconucleated reticulocyte (MN-RET) assay. Following a large radiation challenge dose, cells from mice exposed to CT scans or mice that exercised had significantly less DNA damage (fewer foci) in their bone marrow compared to control mice. Mice that where exposed to CT scans and exercised had significantly lower spontaneous levels of MN-RET compared to control mice. When given large challenge doses, there was a significant reduction in MN-RET levels in mice that where exercised alone or exercised combined with CT scans. Markers of oxidative damage, antioxidant enzyme activity and mitochondrial enzyme activity were measured to assess high dose radiation damage to muscle tissue. The results showed that exercise and CT scans could protect skeletal muscle from exposure to a large challenge dose of radiation. Overall, we have shown that similar mechanisms are induced by CT scans or exercise and protect cells against high doses of radiation indicating that long term risk like cancer formation may be reduced.

NEW EVIDENCE FOR THE PREVENTION OF DIABETES AND ITS COMPLICATIONS BY LDR: POTENTIAL CLINICAL APPLICATION

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Induction of hormesis and adaptive response by low-dose radiation (LDR) has been extensively indicated. Adaptive response induced by LDR was not only resistant to damage caused by subsequently high-dose radiation, but also cross resistant to other non-radiation challenges such as chemicals and even diseases-related oxidative stress. This adaptive response mechanistically was considered due to up-regulated expression of protective proteins such as the various antioxidants. Oxidative stress is a major cause for diabetes and its complications, therefore, this presentation will overview the available data with an emphasis of the preventive effect of LDR on the development of diabetes and its cardiovascular complications. The emerging evidence indicates that pre-exposure to LDR reduced the incidence of alloxan-induced diabetes, delayed the onset of hyperglycemia in diabetes-prone non-obese diabetic mice, and also lowered the blood glucose levels of type 2 diabetes. Experiments with animal models indicated that proper exposure of diabetic animals to LDR could also significantly reduced diabetes-induced damage in the kidney, heart, and brain. In addition, exposure of diabetic animals also accelerated diabetic wound healing, probably via stimulating of stem cells. These results provide strong experimental evidence for the potential beneficial effects of proper application of the hormetic mechanisms induced by LDR on human with diabetes. In addition, this presentation will also provide certain current information regarding the cardiovascular diseases in human populations who were exposed to LDR under various conditions. Although there remains a debate, the updated epidemiological data remains unable to reveal a significant increase in the risk of these diseases for the population who were exposed to radiation at low-dose range. These data are important for us to consider the balance of LDR's potential risk and benefits, particularly for peoples with chronic diseases.

EVALUATION OF ALPHA RADIATION CYTOTOXICITY AND GENOTOXICITY IN A549 CELL LINE

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The decay products of radon emit alpha particles are considered to be the most prominent environmental cause of lung cancer. The scientific community agrees to the need of understanding the mechanisms that lead to a cause-effect relationship between the dose values absorbed by the lungs and the biological effects induced by the exposition. The major adverse consequences of radiation exposures are attributed to DNA damage that has not been correctly restored by metabolic repair processes. Additionally, the estimation of the dose value received by the exposed population is impractical to achieve without using a physical dosimeter.

In this work, we quantified the biological effects induced by alpha radiation, ^{210}Po source in an epithelium human cell line (A549). To quantify the genetic lesions induced by different values of absorbed doses, the cytokinesis blocked micronuclei technique was used. The survival fraction was also quantified using the Clonogenic Assay. The following dose values were used; 0, 50, 100, 500, 1000, 1500 and 2000 mGy. The dose rate of the ^{210}Po source was 30 mGy/min.

The results reveal an increase in the number of DNA damaged cells with enlarged dose values of alpha radiation, which is most evident from the increase frequency of one micronuclei per binucleated cell. For higher doses, i.e. greater than 1000 mGy, the frequency of two micronuclei per binucleated cell undergoes an evident increase. As a one step further possibility, the dose response curve obtained can allow a biodosimetric determination of radon dose to airway cells at cumulative exposures. In terms of fraction of cell survival to alpha radiation exposition, the results obtained show a marked decrease with dose increase. As expected, the percentage of cell survival shows a major disparity when higher doses are applied.

EFFECTS OF LOW-DOSE RADIATION ON CARDIAC DAMAGE AND CARDIOVASCULAR INFLAMMATION

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Cardiovascular protection against diabetes-induced inflammation and damage by multiple exposures to low-dose radiation (LDR) was investigated in order to explore a novel therapeutic approach to diabetic cardiovascular diseases (CVD). C57BL/6J mice were given multiple low-doses of streptozotocin (STZ, 60 mg/kg x 6) to generate a type 1 diabetes. A week after the last dose of STZ, hyperglycemic mice were diagnosed and given with and without whole-body exposure to LDR (25 mGy X-rays) once every other day for 2, 4, 8, 12 and 16 weeks. Diabetes caused significant increases in cardiac and vascular inflammation, shown by time-dependent increases in both mRNA and protein expressions of interleukin-18 (IL-18), tumor necrosis factor-alpha (TNF-α), intercellular adhesion molecule-1 (ICAM-1), and monocyte chemoattractant protein 1 (MCP-1), as well as both pro-inflammatory and pro-fibrotic factor, plasminogen activator inhibitor type 1 (PAI-1) in the heart and aorta. Multiple exposures of non-diabetic mice caused mild increases in these inflammatory factors, except for ICAM-1; however, multiple exposures of diabetic mice to LDR significantly attenuated diabetes-induced increases in IL-18, TNF-α, MCP-1, and PAI-1 except for ICAM-1, at both mRNA and protein expressions in the heart and aorta. In line of cardiovascular inflammation, increases in cardiac histopathological abnormalities, oxidative damage and fibrosis were evident in diabetic mice, effects that were significantly prevented in the diabetic mice with multiple exposures to LDR. These results suggest that LDR, although may cause a slight cardiovascular inflammation, can significantly attenuate diabetes-induced cardiovascular inflammation and cardiac pathological damage so that LDR may become a novel therapeutic approach to prevention of diabetic CVDs.

LOW-DOSE RADIATION ACCELERATES DIABETIC WOUND HEALING LIKELY THROUGH PERIPHERAL MOBILIZATION OF BONE MARROW STEM CELLS

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To develop a novel approach to acceleration of diabetic wound healing, we have investigated the effect of multiple exposures to LDR (75 mGy X-rays) on skin wound healing in diabetic rat model. Diabetes was induced with a single i.p. injection of streptozotocin (50 mg/kg) in Wistar rats, and hyperglycemia was defined 3 days after STZ treatment. Skin wound was made on the back of non-diabetic rats and diabetic rats with persistent hyperglycemia for 60 days. Diabetic rats with skin wound were exposed to whole-body LDR at 75 mGy daily with 2-day interval of break after each five-day exposures. Wound healing size was estimated on day 5, 10 and 15 after skin wound formation among the control group (non-diabetic rats with skin wound treated with saline), diabetic rats with skin wound treated with saline, and diabetic rats with multiple exposures to LDR except for saline. Multiple exposures of diabetic rats to LDR significantly accelerated the skin wound healing as compared to diabetic rats. The improvement of diabetic wound healing by multiple exposures to LDR was associated with an increased bone marrow and circulating stem cells, measured by CD31+ cells with FACS, and increases in wound tissue's vessel regeneration and cell proliferation, measured by microvessel density and proliferating cell nuclear antigen, along with an up-regulation of MMP-2 and MMP-9 mRNA and protein expressions in the wound tissue. These results indicated that multiple exposures of diabetic rats to 75 mGy X-rays significantly accelerated diabetic wound healing, most likely through stimulation of bone marrow stem cell proliferation and peripheral mobilization.

THE HISTORY OF CHEMICAL HORMESIS

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Despite the long history of hormesis-related experimental research, no systematic effort to describe its early history has been undertaken. The present work attempts to reconstruct and assess the early history of such research and to evalutate how advances in related scientific fields affected the course of hormesis-related research. The purpose of this work is not only to satisfy this gap in current knowledge, but also to provide a foundation for the assessment of how the concept of hormetic dose-response relationships may have affected the nature of the bioassay within a modern risk assessment framework.

THE HISTORY OF RADIATION HORMESIS

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This work represents the first systematic effort to describe the historical foundation of radiation hormesis. Spanning the years from 1898 to the early 1940's, this work constructs and assesses the early history of such research and evaluates how advances in related scientific fields affected the course of hormetic-related research. The present effort was designed to not only address this gap in current knowledge, but to offer a toxicological basis for how the concept of hormetic dose-response relationships may affect the nature of the bioassay and its role in the risk assessment process.

USE OF THRESHOLD MODELING TO ESTIMATE HUMAN RELATIVE POTENCIES OF DIOXIN-LIKE COMPOUNDS

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Donor-to-donor variation in human cell cultures often makes dose response modeling a challenge. This is particularly evident when attempting to estimate relative potencies (REPs) for dioxin-like compounds (DLCs). In the current study, large inter-donor variation in the maximal agonist effect for *CYP1A1* induction was seen in normal human epidermal keratinocyte (NHEK) cultures exposed separately to aryl hydrocarbon receptor (AHR) agonists 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), 1,2,3,6,7,8-hexchlorodibenzo-*p*-furan (HxCDF), and 3,3',4,4',5-pentachlorinated biphenyl (PCB 126). Estimation of REPs required a complex mixed-effects Hill model that assumed DLC partial agonism. The accuracy of 50% effective concentration (EC50)-derived REPs using uncertain maximal effects of differing magnitudes would be in doubt. However, the response observed at low agonist concentrations appeared to be extremely consistent across NHEK donor cultures. In fact, log10-transformation of response and concentration revealed a donor-invariant threshold of effect. Following the removal of high concentration data, a continuous piecewise regression model was formulated to directly estimate REPs based upon relative threshold concentrations (i.e., RTCs). This model was "hockey-stick" shaped with an initial slope of zero and then a linear concentration-effect beyond each breakpoint. The resulting threshold concentrations and RTCs were largely invariant, regardless as to whether or not the response slopes were assumed to be parallel among the different AHR agonists. In addition, by simultaneously modeling all three compounds, derivation of an RTC for HxCDF was possible by "borrowing" information across chemicals regarding the location of the baseline expression level. Overall, this threshold modeling procedure for REP derivation can likely be applied to other *in vitro* systems where donor variability in response and/or the presence of partial agonists pose problems. Furthermore, the observation of an AHR-mediated threshold in the current study is entirely consistent with previous observations, both *in vitro* and *in vivo,* of a "switch"-like mechanism for *CYP1A1* induction.

QUANTIFYING THE ROLE OF SEROTONIN IN GENERATING RADIATION INDUCED BYSTANDER EFFECTS

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Serotonin has been shown to be involved in the production of bystander signals by irradiated cells. In this study we examined levels of serotonin in 10 different batches of commercially available fetal bovine serum (FBS) and correlated the serotonin levels with the toxicity of medium harvested from irradiated cells (ICCM) using a standard medium transfer colony forming assay. Serotonin levels in the serum varied widely between batches and the levels correlated directly with the toxicity of the harvested ICCM. Three serum samples had levels of serotonin below 25ng/ml and these did not show medium transfer bystander effects. Exposure of serum samples to normal daylight reduced serotonin levels significantly. We suggest that serum batch variability may underlie much of the inter-laboratory variation in ability to produce bystander effects and further suggest that serum batches are protected from light and prescreened for ability to produce a bystander effect using a positive control cell line. To answer the question of whether there is a limit to the amount of serotonin required to induce a bystander effect in naïve cells, the 5-HT_2 and 5-HT_3 receptors of the serotonin transport system will be competitively inhibited at varying intervals post medium transfer. Ketanserin and Granisetron (respective antagonists for the aforementioned receptors) will be used to inhibit serotonin transport. If a serotonin threshold does exist, then the variation in serotonin levels between batches of FBS would be insignificant as long as it is of a level that accommodates the threshold concentrations. Furthermore our preliminary data suggest, induction of the apoptotic cascade resulting from an intracellular influx of calcium may also be associated with a certain concentration of serotonin and this is currently being verified using a fluorometric calcium flux assay.

RADIATION-INDUCED BYSTANDER EFFECTS AFTER MEDICAL MICROBEAM RADIATION TREATMENT OF RAT BRAIN

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Microbeam radiation therapy (MRT) is a new type of radiosurgery in the pre-clinical stage, developed for brain tumor treatment. MRT uses high-flux synchrotron light delivered as an array of parallel microbeams in high doses of irradiation to tumors in fractions of seconds. Some evidence suggests that MRT gives better clinical results than homogenous field radiotherapy but the mechanism of this effect is unknown. The aim of this study was to investigate the response and the potential adverse effects of MRT and homogenous field on non-irradiated tissue and to analyze the induction of bystander associated proteins, which were expected to occur under this controlled high-doses of irradiation in both brain tissue that is outside of the path of the irradiation array and in a distant organ (bladder).

Healthy adult wistar rats were anaesthesised and exposed to either 35 or 350 Gy MRT or to homogenous field radiation to the right brain hemisphere. The rats were allowed to recover and were kept alive for 4, 8 or 12 hrs, without adverse effects being noticed. Sham controls and scatter dose controls were also included. The brain and bladder were then dissected and samples taken for proteomics and for the bystander reporter assay. The clonogenic survival of reporter HPVG cells fed with growth medium collected from explants showed that bystander effects occurred in both the non-irradiated left brain hemisphere and in the distant bladder tissue, confirming our hypothesis. Proteomic studies are in progress. The results suggest that systemic bystander or abscopal effects may be important to consider if this treatment is proposed for human brain glioma treatment.

EFFECTS OF LOW DOSE THIMEROSAL ON FIBROBLAST IMMUNE RESPONSE GENE EXPRESSION IN PATHWAY-FOCUSED DNA MICROARRAYS

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Low dose thimerosal (TML) is being investigated for potential use as a treatment of virus infections such as those caused by herpes and influenza viruses. Previous research indicated that TML is not acting directly against these viruses. Rather, TML may be promoting an antiviral host response that is immunological in nature. Accordingly, pathway-focused DNA microarrays (Oligo GEArray system, SABiosciences) were used to investigate the effects of TML on immune response gene expression in normal human diploid fibroblasts (HDF cells). Cells were treated with subtoxic concentrations of TML (1.6 - 40 ng/ml) for up to 24 hours, followed by RNA extraction and cRNA production. Samples were screened using arrays containing nucleic acid probes for 400 autoimmune and inflammatory response genes to profile gene expression. TML upregulated about 25 immune response genes of interest. A number of these genes are known to be involved in resistance to virus infections and/or the regulation of inflammatory responses, including IFNGR2, which encodes interferon gamma receptor 2; IL6 and IL8, which encode interleukins 6 and 8, respectively; ANXA1, which encodes annexin A1, an inhibitor of phospholipase A2; CEBPB, a transcription factor; LTA4H, which encodes leukotriene A4 hydrolase; and NFATC4, which encodes a nuclear factor of activated T-cells. Other immune response genes of interest upregulated by TML at more than one concentration or treatment time included MYD88, YY1, CAST, CKLF, PRDX5, SERPING1 and TGFBR2. These results provide insight into the mechanisms through which TML could mediate host immune responses to viral infections.

CANCER MORTALITY IN LOW VERSUS HIGH ELEVATION COUNTIES IN TEXAS

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There is controversy as to whether low levels of radiation (i.e., < 5 rem) pose a significant health risk. With increasing land elevation there is a corresponding increase of natural background radiation. This brief ecological inquiry compares archived cancer mortality in relatively low, medium and high elevation counties in Texas. The mortality data consisted of age-adjusted deaths per 100,000 persons, all sites cancer, both genders, all races, for years 2001-2005, and below the age of 65. The land elevation categories for counties consisted of those having relatively low (0-250 feet above sea level), medium (500-1000 feet above sea level) and high (3000+ feet above sea level) elevations. Cancer mortality was found to be lowest in the high elevation counties (mean = 58.2 deaths per 100,000 persons) followed by low elevation counties (67.5 deaths per 100,000 persons) and then medium elevation counties (70.4 deaths per 100,000 persons). Although this trend was not 100% linear, statistically significant differences in mortality rates (using a two-tailed *t* test) were found only with comparisons involving high elevation counties, that is, between low versus high elevation counties ($p = 0.003$), and medium versus high elevation counties ($p = 0.010$), but not between low versus medium elevation counties ($p = 0.5$). More rigorous research, that includes the case-control design, with an accounting of confounding variables, is indicated.

ALCOHOL SHOW HORMETIC CHARACTERISTICS ON DEVELOPMENT OF ZEBRAFISH EMBRYOS

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Zebrafish (*Danio rerio*) embryos were continuously exposed to different, very low concentrations of ethyl alcohol (EtOH) from 2h of day 1 till day 14 post-fertilization. Forty embryos were grouped into four individual 250 ml beakers by ten. Group one was maintained in egg-water, group two in egg-water containing 0.5% EtOH, group three in egg-water containing 0.1% EtOH and group four in egg-water containing 0.05% EtOH for fourteen days. This experiment was performed according to the protocol that was designed for two preceding experiments that were carried out and published by two different student groups in 2002, 2003 and 2007. The experiment was repeated this time because the findings of previous groups showed EtOH effects that contradicted common sense. In other words, in all cases they found that the lowest EtOH concentration (0.05%) killed most of the embryos in the shortest time, while embryos in the somewhat higher concentrations (0.1% and 0.5% EtOH) all survived till day 14. Contrary to our expectations, in this experiment we also obtained exactly the same results (0.05% EtOH killed 7 embryos by day 2 and by day 10 all embryos died, while 5 and 3 embryos survived in 0.1% and 0.5% EtOH, respectively, till day 14), thus confirming the same phenomenon as the earlier authors. This result raises the possibility that the effect of ethyl alcohol may follow the rule of hormesis, when the bottom of U shape curve of concentration has a less toxic (sometimes even beneficial) effect, a well known phenomenon in toxicity.

AUTOMATING TRADITIONAL ASSAYS USING HIGH CONTENT SCREENING TOOLS

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Traditional assays are often inadequate for low dose radiation research due to the subtlety of the effects being examined. Fully automated micronucleus (MN) AND 53BP1 foci formation assays have been developed. The complete assays, from tissue culture to imaging, are performed in 384 well plates. A Thermo Scientific SP-WorkCell, a fully contained and automated liquid handling robotic workstation, performs the tissue culture and successive cell staining and fixing. The workcell is capable of performing dual immunofluorescence staining on forty 384 well plates (over 15,000 wells) in eight hours. The plates are imaged with a high speed, high resolution Perkin Elmer Opera confocal microplate imager. Approximately 10 wells (5 fields of view, 40x objective) and 1500 (at most, 30,000 foci) can be scored per minute for the 53BP1 assay using Acapella software. The sensitivity of the assays has been tested in MCF-7 and MCF-10A cells treated with gamma irradiation from the Taylor radiobiology Cs-137 source at McMaster University. Low doses ranging from 10-100 mGy and high doses ranging from 1-4 Gy were administered at dose rates of 14.5 mGy/min and 0.25 Gy/min for the low and high doses respectively. The automation of standard assays enables the detection of subtle radiation induced effects through the analysis of large sample sizes. High content image acquisition and automated scoring eliminate human bias due to drift and greatly enhance the statistical power of the assays. High content screening tools can be used for low dose radiation research.

RESISTANCE TO CHEMOTHERAPY EXPLAINED BY HORMESIS

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We describe a potential mechanism for the observation of hormesis in the cellular response to chemotherapeutic agents. This analysis focuses on a recent paper by Yauch *et al*. (2009) describing a missense mutation (*i.e.*, G-to-C in codon 473; His replacing Asp) that conferred drug resistance to medulloblastoma in a patient who experienced a relapse following an initially successful treatment with the Hh antagonist drug GDC-0449. PET scans three months after treatment revealed that the disease had progressed, with the new neoplastic growth having markedly enhanced resistance to GDC-0449. We have described how this enhanced drug resistance displayed a hormetic dose response in an animal (murine) model (Calabrese and Nascarella, *In Press*). This finding has significant implications on: evaluating chemotherapeutic agent dose-responses, selecting an optimal study design, elucidating biological mechanisms, and evaluating disease outcome. Our presentation reveals how a quantitative understanding of the hormetic dose response may be useful in illustrating the limits within which a rebound/relapse effect may occur, significantly affecting subsequent clinical strategies and disease outcome. While this assessment is focused on the important mutational and experimental findings of Yanch *et al*. (2009), it should be recognized that the hormetic dose response is also a central feature in numerous other biomedical endpoints, affecting memory, bone strengthening, wound healing, hair growth, anxiety, seizure responses, neuroprotection, longevity and numerous other endpoints critical to patient care and the public health (Calabrese, 2008).

Key Words: hormesis, biphasic, GDC 0449, medulloblastoma, tumor relapse, hedgehog pathway

References

Calabrese EJ, and Nascarella MA. *In Press.* Tumor Resistance Explained by Hormesis. *Dose-Response*. DOI: 10.2203/dose-response.09-063.Calabrese

Yauch RL, Dijkgraaf GJP, Alicke B, Januario T, Ahn CP, Holcomb T, Pujara K, Stinson, J, Callahan CA, Tang T, Bazan JF, Kan Z, Seshagiri S, Hann CL, Gould SE, Low JA, Rudin CM, and de Sauvage FJ. 2009. Smoothened mutation confers resistance to a hedgehog pathway inhibitor in medulloblastoma. *Science* 326:572-574.

THE FREQUENCY OF HORMETIC RESPONSES IN THE AMES ASSAY

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This study assessed the occurrence of hormetic dose responses from three previously published data sets (Mortelmans et al., 1986, Zeiger et al., 1986, 1988) with 820 chemicals in three Ames assay tester strains (i.e. TA 97, 98, 100) with and without the S9 fraction, using a five dose protocol and semi-log dose spacing. Ninety-five (95) (11.6%) chemicals satisfied the multiple *a priori* entry criteria with a total of 107 dose responses. Of these dose responses, 61 involved TA 100, a strain that detects base-pair substitution mutations. 32.8% (20/61) satisfied the evaluative criteria for hormesis, exceeding that predicted by chance by 4.14 fold ($p < 0.001$). The remaining 46 dose responses involved TA97 and TA98, strains that detect frameshift mutations. 4.4% (2/46) satisfied the evaluative criteria for hormesis. These findings indicate that hormetic dose responses were commonly observed for mutations in the Ames assay but only for base pair substitution and not with frameshift mutations.

KEY WORDS: hormesis, mutagen, mutagenicity, hormetic, U-shaped, J-shaped, dose response, adaptive response

EFFECTS OF ETHANOL ON THE BEHAVIOR OF ZEBRAFISH (*DANIO RERIO*)

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Ethanol (EtOH) often has stimulatory effects at low doses and inhibitory effects at high doses, thus exhibiting a hormetic dose-response curve. At Wagner College, the zebrafish (*Danio rerio*) has been used as a model organism to examine the effects of low levels of EtOH as part of an undergraduate research program. The effects of EtOH on behavior are reviewed here. Typically zebrafish were exposed to the following EtOH concentrations (v/v): 0.0% control, 0.125%, 0.25%, 0.5%, and 1.0%. As expected for hormesis, shoaling (grouping) behavior as measured by nearest neighbor distance exhibited a J-shaped dose-response curve, with the tightest shoals occurring with exposure to low levels of EtOH. Similarly, escape responses of zebrafish appeared to be stimulated at low doses, although this pattern was not statistically significant. Zebrafish also appear to be more active at low doses of EtOH. On the other hand, time to find food in a Y-maze increased at concentrations above 0.25%. Results for species recognition are difficult to interpret. Control zebrafish preferentially approached members of their own species to pearl danios (*D. albolineatus*), as expected. This preference was erased at high doses and reversed at low doses. In addition to adding to the literature on nonlinear dose-response curves, the work reviewed here highlights the usefulness of zebrafish as a model for studying alcohol effects and as a suitable species for research involving undergraduate students.

BIOLOGICAL EFFECTS AND ADAPTIVE RESPONSE FROM SINGLE AND REPEATED COMPUTED TOMOGRAPHY SCANS IN C57BL/6 MICE

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This research is focused on assessing the biological responses associated with diagnostic CT X-rays in a murine model. We investigated the possible presence of an adaptive response induced by single and repeated computed tomography (CT) scans. The endpoints used were: micronucleated reticulocyte (MNRet) formation, histone H2AX phosphorylation, and apoptosis levels. We postulated that through the induction of low level oxidative stress, repeated low dose CT scans (20mGy, 2d/wk, 10wk) could protect mice (C57Bl/6) from acute effects of high dose radiation (1Gy, 2Gy). We also postulated that single CT scans would exhibit detectable biological effects. Repeated CT scans for 10 weeks (total dose 400 mGy) had a significant 12% reduction in MN-RET levels ($p=0.040$) relative to levels in control mice. The same reduction was not evident following a 1 Gy challenge of γ-radiation ($p=0.336$). Significant decreases in γH2AX foci formation following an *in vitro* challenge dose of 1 Gy ($p=0.017$) and 2 Gy ($p=0.026$) was observed in the repeated CT treated mice. Spontaneous apoptosis levels (caspases 3 and 7 activation) were also significantly lower in the repeated CT mice than the non-CT controls ($p<0.001$). In contrast, mice receiving only a single CT scan showed elevated levels of apoptosis ($p<0.02$) and γH2AX foci formation following a 2 Gy challenge ($p<0.05$) compared to corresponding controls. Overall, repeated CT scans seem to confer resistance to larger doses in mice, whereas, single CT scans exhibit characteristics of radiation sensitization.

DOSE RESPONSE OF MENAINV CELLS TO DIFFERENT DILUTIONS OF ARSENIC TRIOXIDE FOLLOWED BY IONIZING RADIATION

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$Mena^{Inv}$ are highly malignant cancer cells derived from MTLn3 cell line from mouse mammary epithelium with elevated expression of Mena genes. Previous studies have demonstrated that MTLn3 are resistant to both chemotherapy and ionizing radiation. In this study $Mena^{Inv}$ cells were exposed to an inorganic chemical, Arsenic Trioxide (As_2O_3), in combination with ionizing radiation to analyze their survival behavior. Cells were treated with a series of concentration of As_2O_3 from low (20μM) and ultra-low ($6x10^{-10}$μM) for 24hr and 58hr. The cells were irradiated to 200 cGy with 6 MeV electrons energy. The post-radiation cell proliferation was quantified by measuring the mitochondrial succinate-tetrazolium reductase. Cell death was observed in the concentrations of As_2O_3 from 20μM through 1.25μM in cells treated with As_2O_3 alone and in combination of As_2O_3 plus radiation. Radiation at the used dose alone had little effect on the cell proliferation. An abrupt cell survival proliferation was seen after the initial cell death. This peak appears to be due to hormesis. The hormesis was observed within the As_2O_3 concentration from 0.625μM to 0.039μM. The combined chemo and radiation treatments of the cells did not affect the hormetic behavior though the survival level was less pronounced. As_2O_3 concentrations from 0.039μM down to ultra-low ($6x10^{-10}$μM) were observed to stimulate cell proliferation uniformly throughout the range. We have demonstrated that specific low concentrations of As_2O_3 can induce cell death in otherwise highly malignant chemo and radiation resistant cancer cells. However this low concentration-mediated cell death is immediately followed by a surge in cell survival. Low dose dosimetry is highly desirable in metronomic therapy though it has a narrow window since necrosis, hormesis, apoptosis and other dose-dependent biological effects take place in this region. Further quantifiable dosimetry is highly desired for routine clinical practice.

PROTEOMIC CHANGES IN THE GILLS OF IRRADIATED AND BYSTANDER WILD TYPE AND TRANSGENIC RADIOSENSITIVE MEDAKA

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Wild type and radiosensitive transgenic medaka were irradiated with 0.5 Gy X-radiation. These fish were used to induce a bystander effect in non-irradiated medaka. The gill proteomes were then examined. Irradiation increased annexin A1, creatine kinase (CK), lactate dehydrogenase (LDH) and complement component C3 (C3) in both strains, reduced annexin A4 in wild type and increased ABC transporter in radiosensitive medaka. In bystander fish, same strain pairings increased CK and LDH in both strains, decreased C3 in wild type and increased annexin A1, annexin A4 and ABC transporter in radiosensitive medaka. In mixed strain pairings annexin A1 was only increased by a bystander signal from a radiosensitive source, annexin A4 was increased in radiosensitive bystander irrespective of the radiosensitivity of the bystander signal source, and CK and LDH were increased if either the signal origin or the recipient fish was radiosensitive. Warm-temperature acclimation related 65 kDa protein (Wap65) was increased in bystander medaka, irrespective of pairing and chromosome 5 SCAF protein were increased in radiosensitive bystander medaka only. Annexin A1, annexin A4, CK, LDH and C3 are associated with apoptosis and mirror the increase in apoptotic bodies previously reported in medaka, whereas increased Wap65 and LDH suggest a protective response against reactive oxygen species and lactate acidosis, respectively. Elements of these responses reflect those seen in rainbow trout. In irradiated trout annexin II is increased whilst in bystander trout hemopexin-like protein and pyruvate dehydrogenase (PDH) are increased. These proteins offer similar protective properties as Wap65 and LDH, respectively. However, whereas bystander trout proteome responses suggest an immediate protective effect only, the apoptosis associated changes to the medaka proteome could indicate both immediate protection and longer term adaptation, suggesting that the bystander signal can override the genetically determined response and that signal production and response can be modulated independently.

PRACTICAL IMPLICATIONS OF NANODOSIMETRY IN CLINICAL MEDICINE

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The quest to manufacture nanoscale drugs to treat common diseases so far has appeared elusive. The grandiose promises made decades ago of cost reduction, miracle cures for cancers and universal availability of nanomedicine are still a far cry. Even we do not have any viable models to exploit nanotechnology in general medicine such as surgery, pharmacology and diagnostics. The urgent need for nanotechnology in medicine is to develop nanoscale drugs for general practice. The nanotechnology is defined as a process to build entities atom-by-atom or molecule-by-molecule in a bottom up fashion. The upper limit for such components is set up to 100 nanometers in metric length. Beyond this length materials generally assume bulkscale properties which are already being exploited in our daily lives. The biological issues associated with nanoscale drugs are far more complex than merely the manufacturing process itself. The current chemo protocols are based on maximum tolerable dose philosophy. Such a dose, when translated into active nanoscale clusters, quantitatively outnumbers the living cells in an average human body. These nanoscale drug issues are discussed in this paper. A theoretical framework for commonly used drug aspirin has been considered as an example. The possible quantum physical effects have also been theoretically evaluated. Further, the amount of drug molecules in a standardized aspirin dose of 100 milligram has been computed into nanoclusters. The calculations show that the processing of a nanoscale drug is a monumental task which requires new types of manufacturing facilities. Also there is a need to develop new protocols to realize the implementation of nanodosimetry in day-to-day pharmaceutical practice. These new protocols need to clearly delineate the dose-response regions for necrosis, hormesis, apoptosis and bystander effects in a biological system for individual drug for routine clinical practice.

THE HORMETIC EFFECT OF CADMIUM AND PHENANTHRENE ON THE ANTIOXIDANT ENZYME ACTIVITIES IN THE EARTHWORM

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The earthworms are a critical component of the soil ecosystem, leading the cycling of nutrients, improving the physicochemical properties, structure, and aggregation of soils, and benefiting microbial processes in general. Cadmium and phenanthrene are frequently found together as contaminants in soil environment. Confirmation of the general phenomenon of hormesis may have significant implications for ecological risk assessment, although the mechanisms that underlie hormesis remain an enigma. In the present study, the activities of catalase (CAT), superoxide dismutase (SOD), Glutathione peroxidase (GSH-PX), phagocytosis activity, and the content of H_2O_2 and malondialdehyde (MDA) were determined in the earthworm *Eisenia fetida* at different concentrations of cadmium and phenathrene. A model-based approach for describing a dose–response relationship incorporating the hormetic effect was applied to the detection and estimation of the hormetic effect of cadmium and phenanthrene on the enzymes activity.The results showed that cadmium alone and its mixture with phenanthrene at low concentration might induce the hormetic effect of CAT, SOD and GSH-PX, which is characterized by an inverted U-shaped dose response. The content of H_2O_2 and MDA were characterized by J-shaped dose response. The maximum hormetic magnitudes were also compared. The presence of hormesis induced by cadmium and its mixture with phenanthrene in the earthworm may be related to activation of adaptive pathways. Model-based approach and careful preliminary experiments are needed for confirming, detecting and estimating the hormesis.

INDUCTION OF DNA DAMAGE BY POSITRON EMISSION TOMOGRAPHY SCANS

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The goal of this project was to investigate low dose ionizing radiation effects associated with exposure to positron emission tomography (PET) scans. Biological effects were evaluated in Trp53+/+ wild type and Trp53+/- heterozygous female mice, following *in vivo* exposure to diagnostic PET (^{18}F-FDG) scans. The short term biological effects following PET scans were evaluated in order to understand the modification of mechanisms that might alter long term cancer risk. Corresponding life-time cancer risk studies are in progress.

The effect of PET scans on DNA damage in bone marrow was investigated in 7-9 week old Trp53+/+ mice using two flow cytometry-based endpoints: micronucleated reticulocyte (MN-RET) formation and histone H2AX phosphorylation (γH2AX). Mice were scanned with 0, 20, 100 or 400 μCi of ^{18}F- FDG corresponding to whole body doses of 0, 12, 58 and 233 mGy, respectively. There was a dose response for MN-RET formation at doses ≥ 100 μCi ^{18}F-FDG. A second group of mice were scanned with 0, 20, 100 or 400 μCi of ^{18}F- FDG and then challenged *in vivo* with a 1 Gy exposure at 24 hours post scan. The PET scan did not appear to modify MN-RET formation induced in bone marrow by the challenge dose. This was also true for γH2AX foci formation for all injection doses except 400 μCi when there was a significant reduction below controls at 24 hours post scan.

PET diagnostic exposures can induce effects in the bone marrow of mice. Depending on the endpoint, they may also induce an adaptive response that modifies the effects of larger radiation exposures but the timing and magnitude of the challenge dose is important. These studies will be useful in interpreting the meaning of short-term biological endpoints with respect to cancer risk.