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IMPLICATIONS FOR TOXICOLOGY, MEDICINE AND RISK ASSESSMENT

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ABSTRACT BOOK

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University of Massachusetts, Amherst, MA

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NON-IONIZING RADIOFREQUENCY FIELDS-INDUCED ADAPTIVE IN MAMMALIAN CELLS

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Ionizing radiation-induced adaptive response (AR) is well documented in scientific literature. Freshly collected and/or cultured human and animal cells that were pre-exposed to an extremely small dose of ionizing radiation (adaptation dose, AD) were found to be less susceptible to the induction of DNA damage induced by the subsequent higher challenge dose (CD) of the same or similar genotoxic agent.

Non-ionizing radiofrequency fields (RF) in the frequency range of 300 MHz to 300 GHz has a significant and positive impact in modern society. A multitude of devices that emit RF are used in medicine, in industry for heating, welding and sealing of plastics and metals, and for a variety of military purposes. A large increase in the number of people exposed to RF occurred with the introduction of wireless communication services (handheld mobile phones as well as the newer personal communication devices that deliver voice, data and images). Several studies were conducted determine the genotoxic potential of *in vitro* and *in vivo* exposure of animal and human cells to RF. There have been a small number of investigations which examined the induction of AR in mammalian cells which were pre-exposed to RF (AD) and subsequently treated with genotoxic agents (CD). This presentation reviews the results from the latter studies and discusses the implications for human health.

HORMESIS TO ENHANCE NEURAL PROGENITOR CELLS VIABILITY

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Stem cell-based approaches provide hope as a potential therapy for neurodegenerative diseases and stroke. One of the major scientific hurdles for stem cell therapy is the poorsurvival rate of the newly formed or transplanted neural stem cells. In this study, we found that low-dose treatment with the Heat shock protein 90 (Hsp90) inhibitor 17-allylamino-17- Demethoxy-geldanamycin (17-AAG), a heavily investigatedanti-cancer drug, prevented neural progenitor cells from either naturally-occurring or stress-induced apoptosis, although itinduced apoptosis at higher doses. This hormesis effect mediated by low-dose 17-AAG is accompanied by activation of multiple cell survival pathways, including the stress response pathway (induction of Hsp70), the MAPKpathway, and the PI3K/Akt pathway. When administered in vivo, 17-AAG led to Akt and glycogen synthase kinase 3b phosphorylation, and more 5-bromo-2-deoxyuridine positive cells in the mouse brain. These findings could have profound implications in stem cell therapy for neurodegenerative diseases and stroke. (supported by a STP award from GHSU and a SDG from AHA)

HORMESIS IN THE MODELING OF LOCALLY IMPLANTED ANTI-CANCER THERAPY

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Localized cancer treatments were suggested as an alternative to chemotherapy to avoid systemic devastation. We provide a unique modeling approach focusing on the fine balance and dynamical forces exerted between two competing populations: Cancer and healthy cells. We report on finding a non-linear dose-response in the model simulating cancer treatment protocol, when treatment is planted at the tumor site. At very low dosages only a few cells in the tumor area are destroyed; this is not a sufficiently effective approach to treatment. Increasing the dose a small amount destroys large areas of tumor, while preserving healthy cells untouched. When the dose is increased further, both tumor and healthy cells are attacked; as dose increases, treatment becomes more deleterious to the system than the tumor itself. The dose response effect of localized anti-tumor treatment can be graphed as an inverted "J" shape, just as reported in biological systems that present hormetic response.

POSTCONDITIONING HORMESIS; MILD STRESS STIMULATES RECOVERY IN CELLS

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Postexposure conditioning, as a part of hormesis, involves the application of a low dose of stress following exposure to a severe stress condition. The beneficial effect of a low level of stress in postconditioning hormesis on the process of recovery will be illustrated by a number of examples from experimental and clinical research. Postconditioning can be classified as homologous or heterologous, respectively, depending on whether the low dose of stress is of the same type or a different type of stress condition in comparison with the initial high dose stress condition. It is of interest to evaluate whether a difference in recovery efficiency can be observed upon application of substances in low dose ranging from homologous to heterologous. The latter research was performed using heat shocked cells in culture post-exposed to a variety of stress conditions in low dose in order to evaluate activation of recovery in terms of an increase in the synthesis of stress proteins. These stress proteins are involved in cellular repair, recovery and defense mechanisms. The degree of similarity in effect of the different stress conditions was established by exposing cells to high doses of the various stress conditions in terms of an overlap in the pattern of induced heat shock protein families. The experimental data indicate that the beneficial effect on recovery of the low dose stress condition is related to the similarity in molecular stress response that the selected stress conditions (used in high and low dose) are able to induce. These observations are in agreement with the similia principle in homeopathy, which implies that substances causing symptoms in healthy biological systems can be used in low dose to treat similar symptoms in diseased biological systems. The relevance of our studies in relation to the homeopathic principle of similarity will be discussed.

PLENARY

Food Safety and Chemophobia
Gordon Gribble, Dartmouth College, Hanover, NH

For Nuclear Accidents, What is the Appropriate Dose-Rate Limit for Remedial Actions?
Jerry Cuttler, Cuttler & Associates Inc., Mississauga, ON, Canada

FOOD CHEMISTRY AND CHEMOPHOBIA

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"Chemophobia" – the irrational fear of chemicals – has led the lay person to conclude that "natural" ("organic") food is inherently safer than food made using modern, safe synthetic pesticides. Incorrect! Nature is not benign! Most probably, all plants, trees, and vegetables produce their own complement of natural pesticides. It is estimated that we ingest 10,000 times more natural than synthetic pesticides, up to 1 - 2 grams per day. Notable examples of natural pesticides are nicotine, caffeine, cocaine, and pyrethrin, all of which have powerful insecticidal properties. Recent examples of natural pesticides have been identified in asparagus, tomato, mint, and marigold. Of even greater concern are the several natural mycotoxins that can infect food. These include aflatoxin, a mold metabolite formed on peanuts and corn known to cause liver cancer, ochratoxin, a ubiquitous mycotoxin produced by the fungi *Aspergillus ochraceus* and *Penicillium verrucosum* that infects cereals, spices, grapes, and coffee, vomitoxin, a mycotoxin that infects grains (wheat, barley, oat, rye, corn) and causes head blight in wheat and ear rot in maize, and the fumonisins, produced by *Fusarium* molds that infect corn, wheat, and other cereals. These toxins are carcinogenic, heptatoxic, and nephrotoxic to man and animals. Complementary to mycotoxins are bacteria (*Listeria, E. coli, Salmonella*) – the real killer in our food. Food-borne bacterial illness in the US results annually in 76 million cases, 325,000 hospitalizations, and 5,000 deaths. In addition to these topics, my presentation will include natural organohalogen compounds and striking examples of "The Dose Makes the Poison."

FOR NUCLEAR ACCIDENTS, WHAT IS THE APPROPRIATE DOSE-RATE LIMIT FOR REMEDIAL ACTIONS?

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The strong earthquake that occurred in the Pacific Ocean near the City of Sendai, Japan, on March 11, 2011, caused an enormous tsunami that damaged the Fukushima-Daiichi Nuclear Plant. Radioactive fission products were released on the populated areas near the plant. The authorities evacuated approximately 90,000 residents from the areas, and are planning to remove large amounts of soil. These remedial actions have caused enormous human suffering and have been incurring very high economic costs. They believe they are protecting the people from a risk of additional cancers by keeping exposures to ionizing radiation as low as reasonably achievable (ALARA). These precautions are based on the linear no-threshold assumption of radiation carcinogenesis, which has been shown to be invalid.

The experience of medical scientists and practitioners since the late 1890s has demonstrated that low radiation doses/levels are not harmful and in most cases produce beneficial health effects. Recent cell biology studies have discovered that DNA undergoes spontaneous damage at an enormous rate. Organisms and their cells have very powerful defenses that prevent and repair DNA damage and remove damaged cells, including cancer cells. Cancer disease develops when the defenses fail to prevent it. Radiation's principal effect is on these defenses. Low radiation doses/levels stimulate the defenses, reducing the incidence of cancer. High doses/levels have the opposite effect. The mitigating actions for the low radiation levels around the Fukushima plant are not beneficial; they create severe emotional stress for the evacuees and a severe penalty for the Japanese economy. Clinical evidence from medical irradiations suggests that changing the dose-rate limit from 20 mSv/year up to 1000 mSv/year would still be safe.

TOXICOLOGY / RISK ASSESSMENT I

Beyond Dose-Response: Concentration-Responses and Food
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Aalt Bast, Maastricht University Medical Centre, The Netherlands

Chemical Hormesis in Plant Pathogenic Fungi and Fungus-Like Oomycete
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Dose Response Molecular Responses to Asbestos and Silica in Human Lung Cells
Brooke Mossman, University of Vermont College of Medicine, Burlington, VT
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Timothy N. Perkins, University of Vermont College of Medicine, Burlington, VT
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Pseudoscientific Aspects of Fine Particulate Matter (PM2.5) Epidemiology, 1993-2012
James Enstrom, University of California, Los Angeles, CA

Tannins: Hormetic Longevity-Triggers or Just Energy-Allocators
Nadine Saul, Humboldt-Universität zu Berlin, Germany
Kerstin Pietsch, Humboldt-Universität zu Berlin, Germany
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Ralph Menzel, Humboldt-Universität zu Berlin, Germany
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BEYOND DOSE-RESPONSE: CONCENTRATION-RESPONSES AND FOOD

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In this contribution, we present some reflections on nutrition and human health. Our focus is on polyphenols.

These food-endogenous compounds have wide physiological effects. At first glance these effects can be characterized as toxic: SH-reactivity, interaction with proline, chelation of iron, and the like. Nevertheless, physiological end-point research indicates that these myriad of toxic effects are indicative of increased human health, partly related to local concentration effects. The health benefits are exemplified for instance in cardiovascular effects as a result of exposure to polyphenols, like prevention of ischemic–reperfusion heart damage, capillary fragility and doxorubicin-induced cardiotoxicity.

These pleiotropic physiological endpoints arise from the above mentioned multitude of possible chemical reactivities.

Although these individual effects are small in comparison with medicinal pharmacological responses, the combination thereof gives rise to increased homeostatic health.

With food-endogenous compounds we are looking at *dose-responses* rather than narrowly-defined molecular interactions.

Food thus requires a much broader scientific research scope with respect to its interactions with human health. This also forces us to rethink the concept of human health which is best characterized as adaptive in nature. Health as the ability to adapt necessitates science to develop global health indices based on a combination of small responses, rather than on specific strong and narrow indicators for benefit.

Overall research into food and human health requires transformation of research traditions.

CHEMICAL HORMESIS IN PLANT PATHOGENIC FUNGI AND FUNGUS-LIKE OOMYCETE

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Although plant diseases can be caused by bacteria, viruses, and protists, most are caused by fungi and fungus-like oomycetes. Intensive use of fungicides with the same mode of action can lead to selection of resistant strains increasing the risk of unmanageable epidemics. In spite of the integrated use of nonchemical plant disease management strategies, agricultural productivity relies heavily on the use of chemical pesticides and biocides for disease prevention and treatment and sanitation of tools and substrates. The term "hormesis" was first used by Southam and Ehrlich (1943) to describe the low-dose stimulation and high-dose inhibition of fungal growth by western red-cedar heartwood extract and many of the first hormesis studies described the effects of multiple chemicals on yeast metabolism. Despite this prominent use of fungi in these early hormesis experiments, the relevance of hormesis in agricultural systems has not been investigated by plant pathologists, until recently. Little is known about the effects of subinhibitory doses of fungicides on the metabolism of fungal plant pathogens and their ability to cause plant diseases. Interestingly, numerous studies have reported fungicide exposure stimulated the radial growth of resistant strains *in vitro* but did not explore stimulation causes. Recent hormesis studies have demonstrated that subinhibitory doses of fungicides and ethanol can stimulate radial growth and pathogenicity in oomycete and fungal strains. This report provides an update on research investigating chemical hormesis on fungal plant pathogens and provides a perspective of its risks to agriculture production and global food supply.

DOSE- RESPONSE MOLECULAR RESPONSES TO ASBESTOS AND SILICA IN HUMAN LUNG CELLS

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Because of the expense and species-specific responses observed in inhalation experiments using particulates, *in vitro* methods are being developed to determine if they can predict pathogenicity. Most published studies use transformed cell lines, ignore the importance of comparisons with known positive and negative controls, and do not include dose-response studies at nontoxic concentrations of agents. Using human mesothelial and bronchial epithelial cells that are targets of asbestos-related cancers, we first examined by gene profiling (Affymetrix and GeneSifter software), the dose and time-dependent effects of crocidolite asbestos on gene expression in LP9 telomerase-immortalized mesothelial cells. Human mesothelial cells were exposed to low (nontoxic) and high (15 and 75 X 10^6 $\mu m^2/cm^2$ equal surface area concentrations) of crocidolite, nonfibrous talc, fine titanium dioxide (TiO_2), or glass beads for 8 or 24 h. Gene changes by asbestos fibers were concentration- and time-dependent. Human primary pleural mesothelial cells also showed the same patterns of increased gene expression by asbestos using qRT-PCR. Nonfibrous talc at low concentrations caused increased expression of 1 gene at 8 h and no changes at 24 h, whereas fine TiO_2 or glass beads caused no changes in gene expression. Subsequent studies using a mixed fiber/particle sample of Libby amphibole at low fiber concentrations showed increases in mRNA levels of 1 gene (MnSOD) at 8 h and 111 gene changes at 24 h compared to crocidolite (29 and 205 changes, respectively). The ontology and patterns of gene expression by crocidolite and Libby amphibole were almost identical. Currently, we are comparing gene and cytokine changes induced by crocidolite, cristobalite silica and amorphous silica in normal human bronchial epithelial cells and BEAS-2B cells. The extent of gene changes is greatest by asbestos vs. cristobalite silica, and amorphous silica was most inactive, indicating the potential applicability of these models for screening of pathogenic particulates.

PSEUDOSCIENTIFIC ASPECTS OF FINE PARTICULATE MATTER EPIDEMIOLOGY, 1993-2012

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Fine particulate matter ($PM_{2.5}$) has been an important public health issue in the United States and California for the past two decades. Two long-term epidemiologic cohort studies published in 1993 and 1995 found a small positive relationship between $PM_{2.5}$ and total (all cause) mortality during the 1980s. The US EPA then established a National Ambient Air Quality Standard (NAAQS) for $PM_{2.5}$ in 1997. This NAAQS has been used to implement multi-billion dollar nationwide regulations designed to reduce $PM_{2.5}$ originating primarily from the burning of fossil fuels. $PM_{2.5}$ regulations have been particularly aggressive in California. The California Air Resources Board (CARB) concluded in 2008 that $PM_{2.5}$ contributes to 18,000 annual "premature deaths" in California, with diesel particulate matter (PM) being responsible for 3,500 of these deaths. Subsequently, CARB approved a complex set of multi-billion dollar diesel vehicle regulations designed to reduce diesel PM. However, California-specific evidence from seven independent sources conclusively shows NO relationship between $PM_{2.5}$ and total mortality in California. Additional epidemiologic evidence, which shows clear geographic and secular variation in $PM_{2.5}$ mortality risk, does not support the original basis for the NAAQS.

Dr. Enstrom will critically examine the scientific validity of the relationship between $PM_{2.5}$ and mortality, with focus on pseudoscientific aspects of $PM_{2.5}$ epidemiology. The following factors will be discussed: lack of access to key databases; the ecological fallacy; failure to consider other pollutants; failure to satisfy causality criteria; failure to consider other competing health risks; and serious ethical issues. Based on these factors, a strong case will be made that the entire scientific basis for the $PM_{2.5}$ NAAQS needs to be reexamined. In the interest of scientific balance, effort will be made to include direct participation by an advocate of the $PM_{2.5}$ NAAQS, such as, Harvard Professor Joel D. Schwartz, a primary initiator of $PM_{2.5}$epidemiology (http://www.hsph.harvard.edu/review/review_fall_05/rvwfall05_schwartz.html).

TANNINS: HORMETIC LONGEVITY-TRIGGERS OR JUST ENERGY-ALLOCATORS?

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Tannins, a subgroup of plant polyphenols, are frequently described as antioxidants and thus beneficial for human health. However, in contrast, prooxidative, toxic, and antinutritional capacities have also been reported. Doesn't this seeming contradiction sound very hormetic? To test this notion, the nematode model organism *C. elegans* was fed with four tannins or tannin building blocks. Dose-response curves for the endpoints lifespan, oxidative and thermal stress resistance revealed that tannic acid and ellagic acid act in a hormetic fashion. It is conceivable that the observed non-hormetic mode of action of the smaller test substances, namely catechin and gallic acid, were due to their inferior protein-precipitating and -binding properties. If the high molecular-weight tannins are deemed to be beneficial in small concentrations, there may also be another side of the coin. Indeed, the lifespan extending concentration of tannic acid resulted in an inhibition of growth and a delayed onset of the reproductive period. This is in line with Thomas Kirkwood's theory, which states that the additional energy required for life prolongation is removed from other sectors, such as growth. Therefore, small concentrations of tannic acid may be limited to acting as an energy allocator in favour of lifespan. It could be argued that this then does not fit the strict definition of hormesis and calls for the question if hormetic longevity can be hailed as beneficial, if an impairment of growth or reproduction is the resultant cost? Or, alternatively, is the term "beneficial" ill-defined within the context of hormesis?

TOXICOLOGY / RISK ASSESSMENT II

Gene Expression Patterns and Adaptive Response as Mechanistic Background of Hormesis
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Promotion of Metabolic Health and Lifespan by Transiently Increasing Oxidative Stress
Michael Ristow, University of Jena, Germany

Dose-Response Assessment for Arsenic: A Case Study for Why the LNT Doesn't Work
Barbara Beck, Gradient, Cambridge, MA
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GENE EXPRESSION PATTERNS AND ADAPTIVE RESPONSE AS MECHANISTIC BACKGROUND OF HORMESIS

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The well-studied animal model, *Caenorhabditis elegans* (Maupas, 1900), was employed to study polyphenol-induced hormetic changes in lifespan. A detailed insight into the underlying mechanism of hormesis was uncovered by applying whole genomic DNA microarray experimentation and mutant lifespan assays over a range of quercetin (Q) concentrations (50, 100, and 200 μM Q). The transcriptional response to Q exposure followed a non-linear mode which highlighted differential signaling and metabolic pathways. Whilst 50 μM Q regulated processes improving the health of the nematodes (e.g. the gene classes *gst*s, peroxidases, lysozymes, all indicative of glutathione metabolism and xenobiotic biotransformation by cytochrome P450), concentrations between 100 and 200 μM extended lifespan and modulated substantially the global transcriptional response. Overrepresented transcripts were notably part of the biotransformation process (gene-classes: *gst*s, *ugt*s, *cyp*s indicative of drug and xenobiotic metabolism): Enhanced catabolism of toxic intermediates contributes to the lifespan extension. Further significant responses included the overrepresentation of *pdz* genes (important for transport, localization and assembly of supramolecular signaling complexes), transcription factors, and vitellogenins. The regulation of transcription, dauer entry, and nucleosome as well as the Wnt[1] and TGFß[2] pathways pointed towards distinct exposure dependant differences in transcription and signaling pathways. Moreover, a circumstantial link between the alteration of the amino acid metabolism, certain degradation processes in the lysosome and longevity was apparent. Overall, the hormesis mechanisms determining longevity in *C. elegans* are more than just an adaptive response: they comprise distinct changes in transcriptional and metabolic pathways.

[1] Wnt proteins play a variety of important roles in embryonic development, cell differentiation, and cell polarity generation

[2] TGFβ (transforming growth factor beta) signaling pathway is involved in many cellular processes in both the adult organism and the developing embryo including cell growth, cell differentiation, apoptosis, cellular homeostasis, and other cellular functions

PROMOTION OF METABOLIC HEALTH AND LIFESPAN BY TRANSIENTLY INCREASING OXIDATIVE STRESS

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Recent evidence suggests that calorie restriction and specifically reduced glucose metabolism induces mitochondrial metabolism to extend life span in various model organisms, including *S. cerevisiae*, *D. melanogaster*, *C. elegans* and possibly mice. In conflict with Harman's free radical theory of aging (FRTA), these effects may be due to *increased* formation of reactive oxygen species (ROS) within the mitochondria causing an adaptive response that culminates in subsequently increased stress resistance assumed to ultimately cause a long-term reduction of oxidative stress. This type of retrograde response has been named mitochondrial hormesis or mitohormesis, and may in addition be applicable to the health-promoting effects of physical exercise in humans and, hypothetically, impaired insulin/IGF1-signaling in model organisms. Consistently, abrogation of this mitochondrial ROS signal by antioxidant supplements impairs the lifespan-extending and health-promoting capabilities of glucose restriction and physical exercise, respectively. In summary, the findings discussed in this review indicate that ROS are essential signaling molecules which are required to promote health and longevity. Hence, the concept of mitohormesis provides a common mechanistic denominator for the physiological effects of physical exercise, reduced calorie uptake, glucose restriction, and possibly beyond.

For details see: Free Radic Biol Med. 2011 Jul 15;51(2):327-36; PubMedID: 21619928

DOSE-RESPONSE ASSESSMENT FOR ARSENIC: A CASE STUDY FOR WHY THE LNT DOESN'T WORK

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The carcinogenicity in humans of ingested inorganic arsenic (Asi) has been well recognized for decades, largely as a result of studies of populations exposed to high concentrations of naturally occurring Asi in drinking water. In general, carcinogenicity is not observed until drinking water concentrations are well above 200 µg/L, typically 400 µg/L and greater, and in studies outside the United States and Europe; meta-analysis suggest no carcinogenicity at approximately 125 µg/L and lower. However, the nature of the dose-response (D-R) relationship remains an important source of debate and discussion. There are many complexities in evaluating the nature of the D-R relationship, such as integrating the role in metabolism (*e.g.*, the role of the trivalent methylated metabolites as compared with that of the parent compound Asi) into D-R and appropriately interpreting the genotoxicity of Asi (*e.g.*, not a point mutagen, but associated with oxidative DNA damage). Nonetheless, there is a confluence of evidence from different sources, including toxicology and genomic studies and epidemiological analyses, that are supportive of a threshold-type D-R and indicate the linear no threshold (LNT) model is an inappropriate paradigm for evaluating the D-R of Asi. The mode of action (MOA) is currently under investigation, but cytotoxicity followed by cellular regeneration and uncontrolled proliferation is the likely MOA for bladder cancer and may represent a common MOA across all tumor types. Studies are also suggestive of a hormetic-type D-R; this is based on several lines of evidence, such as dose-related changes in base excision repair in cells *in vitro* and non-monotonic changes in global gene expression in the mouse bladder *in vivo*. This presentation will provide an overview on the D-R for Asi, with an emphasis on evidence for hormesis in D-R and for cytotoxicity as a MOA, and the lack of evidence for the LNT.

RADIATION

Gene Expression Profiles of Radiation Threshold Effects in *Drosophila melanogaster*
Michael Antosh, Brown University, Providence, RI
David Fox, Brown University, Providence, RI
Nicola Neretti, Brown University, Providence, RI
Leon Cooper, Brown University, Providence, RI

Chronic Radiation Exposure Induces Cellular Adaptive Response in Interventional Cardiologists
Gian Luigi Russo, Institute of Food Sciences, National Research Council, Avellino, Italy
Idolo Tedesco Institute of Food Sciences, National Research Council, Avellino, Italy
Maria Russo, Institute of Food Sciences, National Research Council, Avellino, Italy
Carmela Spagnuolo, Institute of Food Sciences, National Research Council, Avellino, Italy
Maria Grazia Andreassi, Institute of Food Sciences, National Research Council, Avellino, Italy
Eugenio Picano, Pisa, Italy

The New Radiobiology: Returning to Our Roots
Brant Ulsh, Colorado State University, Cincinnati, Ohio

Effect of Low Doses of Low-LET Radiation on the Innate Anti-tumor and Inflammatory Reactions in Radioresistant and Radiosensitive Mice
Ewa Nowosielska, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Aneta Cheda, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Jolanta Wrembel-Wargocka Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Marek K. Janiak, Military Institute of Hygiene and Epidemiology, Warsaw, Poland

Exposures Involving Perturbations of the EM Field Have Non-Linear Effects on Radiation Response and Can Alter the Expression of Radiation Induced Bystander Effects
Carmel Mothersill, McMaster's University, Hamilton, ON
Colin Seymour, McMaster's University, Hamilton, ON

Low-Dose-Radiation Benefits, a New Paradigm
Bobby R. Scott, Lovelace Respiratory Research Institute, Albuquerque, NM

Hormesis and the Adaptive Response
Colin Seymour, McMaster's University, Hamilton, ON
Carmel Mothersill, McMaster's University, Hamilton, ON

GENE EXPRESSION PROFILES OF RADIATION THRESHOLD EFFECTS IN *DROSOPHILA MELANOGASTER*

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We measured the responses to various doses of radiation, in particular at low doses, on the model organism *Drosophila melanogaster* (fruit fly), measuring lifespan and gene expression. Lifespan results indicate a threshold effect, and a gene-centric and pathway-centric analysis of the gene expression results provide insight into the molecular mechanisms underlying the threshold.

CHRONIC RADIATION EXPOSURE INDUCES CELLULAR ADAPTIVE RESPONSE IN INTERVENTIONAL CARDIOLOGISTS

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Invasive cardiologists are the most exposed to ionizing radiation among health professionals and show an increased rate of somatic DNA damage. Recent studies suggest that cumulative professional radiological exposure is associated with a non-negligible lifetime attributable risk of cancer for the most exposed contemporary cardiac catheterization laboratory staff. On the other side, dated evidence suggest that radiations, induced by very low doses of X-rays, can make human lymphocytes less susceptible to the genetic damage manifested as chromatid breakage induced by a subsequent high dose of X-rays. We evaluated the effects of chronic low dose exposure to ionizing radiation on redox state and apoptotic activation on a healthy population of exposed interventional cardiologists and an age and gender matched unexposed controls. Exposed subjects had a median exposure of 4 mSv/year (range 1-8) by film badge dosimetry (below lead apron) and showed a threefold increase in plasma levels of hydrogen peroxide and a 1.7 fold increase in GSH in erythrocytes. In addition, exposed subjects also showed higher values of caspase-3 activity in isolated lymphocytes, both at baseline and - more strikingly - following high dose radiation challenge. We concluded that in interventional cardiologists, chronic exposure to low dose radiation is associated with an altered redox balance mirrored by an increase hydrogen peroxide and with two possibly adaptive cellular responses: 1) an enhanced antioxidant defence (increase in GSH, counteracting increased oxyradical stress) and 2) an increased susceptibility to apoptotic induction which might efficiently remove genetically damaged cells. In vitro and ex vivo models have been recently established in our laboratory to investigate the molecular mechanisms of cellular adaptation to low-dose radiations exposure.

THE NEW RADIOBIOLOGY: RETURNING TO OUR ROOTS

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In 2005, two expert advisory bodies examined the evidence on the effects of low doses of ionizing radiation. The U.S. National Research Council concluded, "…current scientific evidence is consistent with the hypothesis that there is a linear, no-threshold dose-response relationship between exposure to ionizing radiation and the development of cancer in humans". The French National Academies of Science and Medicine concluded, "…it is not justified to use the linear no-threshold relationship to assess the carcinogenic risk of low doses observations made for doses from 0.2 to 5 Sv since for the same dose increment the biological effectiveness varies as a function of total dose and dose rate". These contradictory conclusions may stem from an emphasis on epidemiological data (a "top down" approach) versus an emphasis on biological data (a "bottom up" approach). Building on several decades of earlier research, the past seven years since these two reports were published have yielded a wealth of radiobiology studies that are revealing qualitative differences between the responses of biological systems at low-doses and dose rates compared to responses observed at high doses and dose-rates. There is increasing evidence of nonlinear responses of biological systems to low radiation doses delivered at low dose-rates, and this talk will review some of these recent studies. This growing body of evidence is casting ever more doubt on the extrapolation of risks observed at high doses and dose-rates to estimate risks associated with low doses dose-rates. The strengths and limitations of the top down and bottom up approaches will be discussed, and proposals for strengthening and reconciling them will be suggested.

EFFECT OF LOW DOSES OF LOW-LET RADIATION ON THE INNATE ANTI-TUMOR AND INFLAMMATORY REACTIONS IN RADIORESISTANT AND RADIOSENSITIVE MICE

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BALB/c than C57BL/6 mice differ in their susceptibility to ionizing radiation, the former being more radiosensitive than the latter. Also, the incidence of cancer following irradiation of the mice with medium doses of ionizing radiation is more frequent in the former than the latter animals. In this study we evaluated the effects of ten equal X-ray irradiations of mice from the two strains on cytotoxic activities of cells involved in the innate anti-tumor surveillance and the development of the induced tumor colonies.

NK cell-enriched splenocytes (NK cells) and peritoneal macrophages (Mφ) were collected from BALB/c or C57BL/6 mice exposed to fractionated irradiations with 0.01, 0.02, or 0.1 Gy X-rays (five days per week for 2 weeks; total absorbed doses of 0.1, 0.2, and 1.0 Gy, respectively). On the selected days after completion of the exposures cytotoxic activities of NK cells and Mφ and production of nitric oxide (NO) by Mφ were assayed. In addition, two hours after completion of the irradiations BALB/c or C57BL/6 mice were intravenously injected with L1 sarcoma and Lewis Lung Carcinoma cells, respectively, and 14 days later the developed tumor colonies were counted on the surface of the lungs.

NK cells collected from all the irradiated BALB/c or C57BL/6 mice demonstrated comparable upregulation of their cytotoxic function which was, for the most part, dependent on the perforin- and FasL-mediated mechanisms. Likewise, Mφ collected from both strains of the mice exhibited the similarly stimulated anti-tumor cytotoxicities and produced significatly more NO following exposures of the animals to all the three total doses of fractionated X-rays. Finally, in both strains of the mice the repeated irradiations with X-rays significantly reduced the number of the induced tumor colonies in the lungs.

The obtained results indicate that ten irradiations with low-level X-rays comparably stimulate the assayed anti-tumor reactions in the BALB/c and C57BL/6 mice.

EXPOSURES INVOLVING PERTURBATIONS OF THE EM FIELD HAVE NON-LINEAR EFFECTS ON RADIATION RESPONSE AND CAN ALTER THE EXPRESSION OF RADIATION INDUCED BYSTANDER EFFECTS

Carmel Mothersill, Department of Medical Physics and Applied Radiation Biology, McMaster University, Hamilton, Canada
Colin Seymour, Department of Medical Physics and Applied Radiation Biology, McMaster University, Hamilton, Canada

Our recent data suggest that the alternative medicine techniques such as Reiki and acupuncture altered the response of cells to direct irradiation and either altered bystander signal production or altered the response of cells receiving bystander signals. Our proposed mechanism to explain these findings is that perturbation of electromagnetic (EM) fields is central to the induction of low radiation dose responses especially non-targeted bystander effects. In this presentation we review the alternative medicine data and other data sets from our laboratory which test our hypothesis that perturbation of biofields will modulate radiation response in the low dose region. The other data sets include exposure to MRI, shielding using lead and or Faraday cages, the use of physical barriers to bystander signal transmission and the use of membrane channel blockers. The data taken together strongly suggest that EM field perturbation can modulate low dose response and that in fact the EM field rather than the targeted deposition of ionizing energy in the DNA may be the key determinant of dose response in a cell or organism The results also lead us to suspect that at least when chemical transmission is blocked, bystander signals can be transmitted by other means. Our recent experiments suggest light signals and volatiles are not likely. We conclude that alternative medicine and other techniques involving electromagnetic perturbations can modify the response of cells to ionizing radiation and can induce bystander effects similar to those seen in medium transfer experiments. In addition to the obvious implications for mechanistic studies of low dose effects, this could perhaps provide a novel target to exploit in radiation protection and in optimizing therapeutic gain during radiotherapy.

LOW-DOSE-RADIATION BENEFITS, A NEW PARADIGM

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Our hormetic relative risk (HRR) model for radiation-related cancer now includes a benefit function, $B(x)$ (Scott BR. Dose-Response 9:444-464, 2011), representing the probability for radiation activated natural protection (ANP) after exposure to a low dose x of radiation. A benefit may be derived when sparsely ionizing radiation types such as X rays, gamma rays, and beta radiation are involved (even if combined with more biologically effective alpha particles). For residential radon exposure (where both alpha and gamma radiations are involved), a significant radiation benefit is the prevention of lung cancers caused by cigarette smoke carcinogens and other environmental agents (Scott 2011). The overall benefit is calculated as the product $B(x)PROFAC$, where the protection factor ($PROFAC$) is the conditional probability that the benefit of interest (e.g., lung cancer prevention) will occur, given that radiation ANP has occurred with probability $B(x)$. Interestingly, everyone seems to benefit [$B(x) = 1$] from residing long-term in homes with an average radon level at or near the Environmental Protection Agency's action level of 4 picocuries/L of air (approximately 150 Bq/cubic meter of air). At a somewhat lower or somewhat higher level of radon, $B(x)$ goes to zero (no benefit). The increase in lung cancer risk as the level of radon increases to somewhat above the action level appears to be mainly related to the loss of radon-exposure-related ANP against lung cancer caused by other agents (Scott 2011). The claim by the Environmental Protection Agency (EPA) that residential radon is responsible for about 21,000 lung cancer deaths every year is therefore not supported by these findings. Instead, residential radon at or near the EPA's action level appears to prevent lung cancer caused by cigarette smoke carcinogens and other agents. This research was supported by the Office of Science (BER), U.S. Department of Energy, Grant No. DE-FG02-09ER64783.

HORMESIS AND THE ADAPTIVE RESPONSE

Colin Seymour, Department of Medical Physics and Applied Radiation Biology, McMaster University, Hamilton, Canada
Carmel Mothersill, Department of Medical Physics and Applied Radiation Biology, McMaster University, Hamilton, Canada

This paper will examine the relationship between hormesis and the adaptive response. The hormetic response has usually been characterized by concentration rather than time, but the adaptive response has been characterized by both dose (concentration) and time interval between doses. Sequential treatments of both radiation and pharmaceuticals are routine for disease treatment.

An analysis will be undertaken to determine whether common mechanisms may occur for both effects. In the same way that a toxic response can be mitigated by repeated dosage through the process of adaptation, can the adaptive response modify the initial hormetic effects through repeated dosage ?

POSTER SESSION

Flawed Human Health Effects Epidemiology: The California Air Resources Board's Diesel Truck Emission Rules
Jerome Arnett, Jr., The Heartland Institute, Chicago, Ill.

Interactions of Low-Dose Radiation and the Carcinogen Benzo[a]pyrene in A/J Mice
Veronica R. Bruce, University of New Mexico, Albuquerque, NM and Lovelace Respiratory Research Institute, Albuquerque, NM
Steve Belinsky, Lovelace Respiratory Research Institute, Albuquerque, NM
Katherine Gott, Lovelace Respiratory Research Institute, Albuquerque, NM
Thomas March, Consultant Veterinary Pathologist, Albuquerque, NM
Bobby Scott, Lovelace Respiratory Research Institute, Albuquerque, NM
Julie Wilder, Lovelace Respiratory Research Institute, Albuquerque, NM

Hormesis and the Salk Polio Vaccine
Edward J. Calabrese, University of Massachusetts, Amherst, MA

Key Historical Studies Serving as the Basis for the Linear Dose Response Challenged
Edward J. Calabrese, University of Massachusetts, Amherst, MA

Production of Cytokines by Splenocytes and Macrophages after Single or Fractionated Low-Level Irradiations with X-rays
Aneta Cheda, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Ewa M. Nowosielska, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Jolanta Wrembel-Wargocka Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Marek K. Janiak Military Institute of Hygiene and Epidemiology, Warsaw, Poland

The Role of X-rays In The Treatment Of Gas Gangrene: A Historical Assessment
Edward J. Calabrese, University of Massachusetts, Amherst, MA
Gaurav Dhawan University of Massachusetts, Amherst, MA

Shifting the Paradigm in Radiation Safety
Mohan Doss, Fox Chase Cancer Center, Philadelphia, PA

Bystander Signal Propagation via Serotonin-mediated Calcium Uptake
Jennifer Fazzari, McMaster University, Hamilton, ON, Canada
Anna Mersov, McMaster University, Hamilton, ON, Canada
Colin Seymour, McMaster University, Hamilton, ON, Canada
Carmel Mothersill, McMaster University, Hamilton, ON, Canada

Revisiting Assumptions of Linearity for Radiation-Induced Cancer: Implications for Chemical Cancer Risk Assessment
R. Golden, ToxLogic LLC, Potomac, MD USA
E. Calabrese, University of Massachusetts, Amherst, MA USA

Cancer Mortality, Natural Background Radiation, and other Selected Predictors
John Hart, Sherman College of Chiropractic, Spartanburg, SC
Seunggeun Hyun, University of South Carolina Upstate, Spartanburg, SC

Effect of Internal Contamination with HTO on the Innate Anti-Tumour and Inflammatory Reactions in Mice
Ewa M. Nowosielska, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Aneta Cheda, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Jolanta Wrembel-Wargocka Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Marek K. Janiak Military Institute of Hygiene and Epidemiology, Warsaw, Poland

Threshold Doses of Single or Fractionated X-rays for Stimulation of Natural Anti-Neoplastic Cells in Mice
Ewa M. Nowosielska, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Aneta Cheda, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Jolanta Wrembel-Wargocka Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Marek K. Janiak Military Institute of Hygiene and Epidemiology, Warsaw, Poland

Low-Dose Gamma Irradiation Inhibits IL-6 Secretion from Fibroblasts that Promotes HBEC Transformation by Cigarette Smoke
Wenshu Chen, Lovelace Respiratory Research Institute, Albuquerque, NM
Xiuling Xu, Lovelace Respiratory Research Institute, Albuquerque, NM
Lang Bai, Lovelace Respiratory Research Institute, Albuquerque, NM
Mabel T. Padilla, Lovelace Respiratory Research Institute, Albuquerque, NM
Bobby R. Scott, Lovelace Respiratory Research Institute, Albuquerque, NM
Yong Lin, Lovelace Respiratory Research Institute, Albuquerque, NM

Non-Targeted Radiation Effects with High Dose Rate (HDR) Brachytherapy
Christine Pinho, McMaster University, Hamilton, Ontario, Canada
Ranjan K. Sur, Juravinski Cancer Centre, Hamilton, Ontario, Canada
Raimond Wong, Juravinski Cancer Centre, Hamilton, Ontario, Canada
Carmel Mothersill, McMaster University, Hamilton, Ontario, Canada
Colin Seymour, McMaster University, Hamilton, Ontario, Canada
Joseph E. Hayward, Juravinski Cancer Centre, Hamilton, Ontario, Canada
Thomas J. Farrell, Juravinski Cancer Centre, Hamilton, Ontario, Canada

Biphasic Dose Responses to Phytoestrogens: An Evaluation of Mechanisms
Miles A. Sarill, University of Massachusetts, Amherst, MA
Edward J. Calabrese, University of Massachusetts, Amherst, MA

FLAWED HUMAN HEALTH EFFECTS EPIDEMIOLOGY: THE CALIFORNIA AIR RESOURCES BOARD'S DIESEL TRUCK EMISSION RULES

Jerome Arnett, Jr., MD. The Heartland Institute, Chicago, Ill.

Regulation cannot be effective if it is based on flawed science. All available scientific evidence shows diesel PM 2.5 does not cause premature death in California, or elsewhere in the United States. Instead of supporting causality, the weak associations found in the epidemiological studies used are probably fortuitous, the result of chance or random variations found in populations, or the result of unknown confounding factors, methodological artifact, and/or biases. Because CARB, EPA, and other state and federal agencies use flawed science and methodology, tens of billions of dollars and hundreds of thousands of jobs have been lost annually, and the health of Americans, instead of improving, has suffered because of the resultant joblessness and loss of wealth. In order to correct the serious, widespread problem with research in human health effects and in epidemiology, scientists, journal editors, and funding agencies should follow a protocol that specifies how they evaluate the data from studies to be published. Among other requirements, the studies must be designed to avoid outcome bias, and an RR value of at least 3.0 to 4.0 must be used in order to suggest causation. All study data sets must be made freely available for review. An educational public relations campaign should be conducted to educate a public that largely has been misinformed or misled. It should emphasize the uncertainties of human health claims and studies and should identify what has been proven by good science, what is uncertain, and what is still unknown.

INTERACTIONS OF LOW-DOSE RADIATION AND THE CARCINOGEN BENZO[A]PYRENE IN A/J MICE

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Low-dose radiation (LDR) activates the immune system and may lead to lung cancer suppression. We investigated the effects of low doses of radiation combined with the carcinogen, Benzo[a]pyrene (B[a]P), in A/J mice. Mice were injected i.p. with B[a]P four weeks prior to exposure to gamma irradiation (10 or 100mGy) at 2 week intervals for a total of 6 doses. After 46 weeks, lungs were examined for cancerous lesions. It was found that irradiation with 100mGy (600mGy total) in combination with B[a]P significantly reduced adenomas in comparison to animals receiving B[a]P only. To elucidate mechanisms that may accompany the reduction in B[a]P induced lung carcinogenesis by LDR, we examined the short-term effects of B[a]P and LDR alone or in combination. Mice were exposed to a single gamma radiation dose (10, 100, or 1000mGy) one day prior to i.p. injection with B[a]P or vehicle. On days 2, 7, or 14, lung and spleen tissues were harvested to determine viable cell counts and phenotype. Splenocytes were cultured for 48 hours +/- Concanavalin A and cytokine secretion was measured. B[a]P injection acted as a cytotoxic as well as a proinflammatory stimulus. It induced a loss of both lung and spleen cell number within one day of injection. It also induced losses in B cells and DCs while increasing lung neutrophilia. High dose (1000mGy) radiation also reduced spleen cell numbers, B cells and T cells. B[a]P induced pro-inflammatory cytokine secretion: IL-1beta, IL-6, IL-17, and MIP-1alpha. In contrast, 10mGy radiation induced IL-4 and IL-10 cytokines, while both 10 and 100mGy doses induced IL-2, none of which are considered inflammatory. These data suggest that low dose radiation may mitigate the inflammatory milieu induced by B[a]P and suppress lung tumor progression.

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HORMESIS AND THE SALK POLIO VACCINE

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The production of the Salk vaccine polio virus by monkey kidney cells was generated using the synthetic tissue culture medium, Mixture 199. In this paper's retrospective assessment of this process, it was discovered that Mixture 199 was modified by the addition of ethanol to optimize animal cell survival based on experimentation that revealed a hormetic-like biphasic response relationship. This hormesis-based optimization procedure was then applied to all uses of Mixture 199 and modifications of it, including its application to the Salk polio vaccine during preliminary testing and in its subsequent major societal treatment programs.

KEY HISTORICAL STUDIES SERVING AS THE BASIS FOR THE LINEAR DOSE RESPONSE CHALLENGED

Edward J. Calabrese, Ph.D., Environmental Health Sciences, University of Massachusetts Amherst

In his Nobel Prize Lecture of December 12, 1946 Hermann J. Muller argued that the dose response for radiation induced germ cell mutations was linear and that there was "no escape from the conclusion that there is no threshold". However, assessment of correspondence between Muller and Curt Stern one month prior to his Nobel Prize Lecture reveals that Muller knew the results and implications of a recently completed study at the University of Rochester under the direction of Stern which directly contradicted his Nobel Prize Lecture. This finding is of historical importance since Muller's Nobel Lecture gained considerable international attention and is a turning point in the acceptance of the linearity model in risk assessment for germ cell mutations and carcinogens.

PRODUCTION OF CYTOKINES BY SPLENOCYTES AND MACROPHAGES AFTER SINGLE OR FRACTIONATED LOW-LEVEL IRRADIATIONS WITH X-RAYS

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Natural killer (NK) lymphocytes and activated cytotoxic macrophages are primary effectors of the anti-tumor surveillance system. Tumoricidal activities of these cells consist in non-specific recognition and killing of neoplastic cells through secretion of cytolytic factors and cytokines that either directly induce apoptotic cell death or stimulate cytotoxic function of other effector cells. In view of this, the aim of the present study was to assess the effects of irradiations with low and higher doses of X-rays on the production of the selected cytokines involved in the innate lymphocyte- and macrophage-mediated cytotoxicity.

For the investigation, splenocytes and peritoneal macrophages (Mϕ) were collected from BALB/c mice pre-exposed to single irradiations with 0.1, 0.2, or 1.0 Gy X-rays, or irradiated for five days per week for 2 weeks at 0.01, 0.02, or 0.1 Gy X-rays (total absorbed doses of 0.1, 0.2, and 1.0 Gy, respectively). Production of IL-1β, IL-2, IL-12, IFN-γ, and TNF-α by these cells in culture was examined using the respective ELISA assays.

The result demonstrated that both single and ten daily irradiations with 0.1, 0.2, or 1.0 Gy total doses markedly stimulated production of IL-2 by splenocytes and of IFN-γ by NK cell-enriched splenocytes. Likewise, secretion of IL-1β, TNF-α, and IL-12 by Mϕ co-cultured with tumor target cells markedly increased after single or fractionated exposure of mice to all the three total doses of X-rays.

Collectively, these results indicate that both single and fractionated exposures of mice to low (0.1 and 0.2) and higher (1.0 Gy) total doses of X-rays stimulate synthesis of cytokines responsible for anti-tumor functions of lymphocytes (IL-2, IFN-γ) and activated macrophages (IL-1β, IL-12, TNF-α).

THE ROLE OF X-RAYS IN THE TREATMENT OF GAS GANGRENE: A HISTORICAL ASSESSMENT

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Gas gangrene is a progressive and often fatal disease caused mainly by the bacterium *Clostridium welchii* (now known as *Clostridium perfringens*) and most commonly associated with car accidents, war wounds, necrotizing myositis, debridement and amputation. Currently employed treatments include surgery, antibiotics, and hyperbaric oxygen. While the use of x-rays to treat patients with gas gangrene ended in the early 1940's with the advent of antibiotics, x-ray treatment had been widely accepted as a useful and highly effective treatment for this condition. The belief that x-rays could be effectively used to treat gas gangrene originated with James F. Kelly in the late 1920's who amassed 364 cases of x-ray treatment of gas gangrene with mortality rate of 11.5% as compared to a mortality rate of nearly 49% with standard treatments. Kelly used a dosage of 150 rads/day in two doses of 75 rads each or three doses of 50 rads each for a 3 minute period and a voltage range of 90-100 kV on an extremity and 130-160 kv on the trunk. Further research is needed to clarify whether the effect of low dose x-rays is due to mechanisms like enhanced localized inflammation, increased production of oxygen free radicals, enhancement of broad spectrum of immune responsiveness or induction of anti-inflammatory phenotype. Nonetheless, low cost and easy availability of x-rays may be a useful option in poor countries that bear the greatest burden of this disease, treating many patients who are unable to afford surgeries, antibiotics, and hyperbaric oxygen.

SHIFTING THE PARADIGM IN RADIATION SAFETY

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The current radiation safety paradigm using the linear no-threshold (LNT) model is based on the premise that even the smallest amount of radiation may cause mutations increasing the risk of cancer. Autopsy studies have shown that the presence of cancer cells is not a decisive factor in the occurrence of clinical cancer. On the other hand, suppression of immune system more than doubles the cancer risk in organ transplant patients indicating its key role in keeping occult cancers in check. Low dose radiation (LDR) elevates immune response, and so it may reduce rather than increase the risk of cancer. LNT model pays exclusive attention to DNA damage, which is not a decisive factor, and completely ignores immune system response, which is an important factor, and so is not scientifically justifiable. In view of the large year-to-year variation in cancer incidence rates, lifetime cancer risk assessments are likely to have large uncertainties from the compounding of these variations. Hence, specifying no threshold, and implying that the smallest calculated increment in cancer risk is significant, is not credible. By not recognizing the importance of the immune system in preventing cancer, and not exploring exercise intervention in the 1970s, the paradigm may have missed an opportunity to reduce cancer deaths among atomic bomb survivors. The paradigm may have failed in its primary responsibility of protecting the health of the irradiated population, and so must be replaced with one that recognizes the body's defense mechanisms. Since LDR stimulates antioxidant levels, LDR may be helpful in reducing aging-related non-cancer diseases, adverse side effects of standard cancer therapies, and inactivity related diseases in the infirm, since oxidative damage is implicated in these. A paradigm shift is warranted to reduce further casualties, reduce fear of LDR, and enable investigation of potential beneficial applications of low dose radiation.

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BYSTANDER SIGNAL PROPAGATION VIA SEROTONIN-MEDIATED CALCIUM UPTAKE

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Based on the evidence of that Serotonin has been shown to be involved in the production of bystander signals by irradiated cells, further investigation into the mechanism of action of this signaling amine is necessary. Based on the serotonin mediated calcium channels…the effect of blocking these channels is monitored through ratiometric calcium measurements of individual cells in culture in response to irradiated conditioned medium. Several 5-HT receptor antagonists were used to block these channels. Granisetron (5-HT3) and Ondansetron (5-HT3) were used to inhibit serotonin transport. The interest in these drugs also stems from their use in porphylaxis of radiation-induced nausea and vomiting and elucidation of possible further interaction with radiation-induced effects is warranted. Ketanserin (5-HT2) was also tested to inhibit an additional 5-HT receptor, 5-HT2. Paroxetine was also used as a general Selective Serotonin Reuptake Inhibitor (SSRI). Un-treated HPVG cultures were irradiated with 0Gy or 0.5Gy by a Cs137 gamma source and left for 1 hour prior to media collection. HPVG cell cultures were plated in glass bottomed culture dishes. 24 hours after incubation at 37C plates were incubated for 15 minutes with the respective concentration of 1 of the 3 drugs followed by the standard ratiometric calcium assay protocol of preparation and measurement. Un-treated reporter cultures were used as a control. Calcium fluxes are to be analyzed for the presence or absence of characteristic peaks in calcium fluxes after addition of ICCM. The calcium peak was abolished after incubation with Granisetron and Paroxetine, however, lower concentrations are being tested based on potential toxicity. Drug toxicity will be assessed using an Alamar Blue viability assay.

REVISITING ASSUMPTIONS OF LINEARITY FOR RADIATION-INDUCED CANCER: IMPLICATIONS FOR CHEMICAL CANCER RISK ASSESSMENT

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HYPOTHESIS Because the linear no threshold (LNT) model used for chemical cancer risk assessment is explicitly based on radiation carcinogenesis data new findings about these data suggest that the LNT
default be reexamined.

METHODS An assessment approach involving reanalysis of relevant data on radiation carcinogenesis, including recently discovered documents in the DOE archives and publications by Calabrese (2011), challenges the basis of the LNT model by showing that it rests on questionable experimental data. If the foundation of linearity for radiation carcinogenesis is unreliable, so must be the regulatory structure built on it for chemical risk assessment. This presentation describes the controversy about the low-dose radiation studies, the history of the NAS Safe Drinking Water Committee (SDWC), and the process which led to endorsing the LNT model.

RESULTS Reanalysis of historical and new radiation carcinogenesis data reveals that the linear concept was highly uncertain with the threshold issue the subject of substantial debate. This involved an influential advocate of the no-threshold concept, radiation geneticist and Nobellaureate H.J. Muller. Because none of this was known in 1977 the SDWC embraced the LNT and endorsed a similar approach for chemical cancer risk assessment. Reconsideration of the LNT concept is timely given recent NAS reports (Applications of Toxicogenomic Technologies to Predictive Toxicology & Risk Assessment & Toxicity Testing in the 21st Century: A Vision & a Strategy). The methods envisioned in both reports permit a more sophisticated ability to experimentally examine the shape of dose response curves for radiation and chemicals with greater precision.

CONCLUSION While prudent in 1977 to use the LNT model for cancer risk assessment, questions about the underlying basis for this decision now casts doubt on key assumptions. Given advancements in toxicology over the past 30 years for understanding thresholds and dose-related transitions these methods should serve as the basis for evidence-based cancer risk assessment.

CANCER MORTALITY, NATURAL BACKGROUND RADIATION, AND OTHER SELECTED PREDICTORS

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This ecological study compares mean 2002-2006 age-adjusted cancer mortality rates in the U.S. to the component of natural background radiation that is based on land elevation (NBR-LE). This relationship is compared to relationships derived from eight other variables commonly thought of as predictors or causes of cancer. These eight predictors, in 2003, are: 1) percent of smokers, 2) percent who had attained a high school diploma or higher, 3) percent who lacked health insurance, 4) per capita income, 5) percent considered as obese, 6) percent who rated their health as excellent, 7) percent who performed physical activity at least 20 minutes, three times per week, and 8) percent who consumed fruits and vegetables at least five times per day. Among the seven predictors considered appropriate for linear multiple regression, only three were found to be statistically significant. Larger t values were considered to show stronger predictions than smaller t values. A negative sign on the t value indicates an inverse relationship while no sign, meaning a positive sign, indicates a direct relationship. From strongest to weakest, these three predictors were: 1) NBR-LE ($t = -3.86$, $p = 0.000$); 2) smoking ($t = 3.61$, $p = 0.001$); and 3) educational attainment ($t = -3.37$, $p = 0.002$). Analysis without outliers (all of which as a side-note were observed in the District of Columbia) did not change the relative strengths of these three predictors and statistical significance remained essentially unchanged. The findings for the well-known predictors were expected. What was unexpected is that the not-so-well-known predictor NBR-LE showed the strongest prediction among the well-known predictors. The inverse finding for NBR-LE suggests the presence of radiation hormesis. Since this is an ecological inquiry, where populations rather than known individual exposures are studied, causal inference is not claimed.

EFFECT OF INTERNAL CONTAMINATION WITH HTO ON THE INNATE ANTI-TUMOUR AND INFLAMMATORY REACTIONS IN MICE

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One of the significant sources of internal radiation exposure of workers and members of the public is tritium, a β^--emitting isotope of hydrogen that binds with hydroxyl radicals to form the easily internalized tritiated water (HTO).

The most important late effect of the low-level exposures to low-LET radiation is development of malignancies. This also applies to HTO which, when deposited in the body of laboratory animals, can instigate tumour growth.

Thus, we aim in the present project, granted by the Polish National Science Centre, to estimate whether internal contamination of mice with HTO can modify the development of pulmonary tumour metastases and whether this effect can be associated with alterations in the anti- or pro-neoplastic functions of macrophages and NK lymphocytes.

The studies will be carried out on two strains of mice (BALB/c and C57BL/6) that differ in their sensitivity to ionizing radiation and whose pro-inflammatory and macrophage-type responses are differently expressed. Mice will be intraperitoneally injected with HTO at such activities that the total absorbed doses of radiation delivered to a mouse will be 0.01, 0.1 or 1.0 Gy; control mice will be injected with PBS. Starting on day 7 post-injection the following parameters will be assessed: cytotoxic activity of NK cells, nitric oxide production by macrophages (as a marker of cytolytic function of these cells against susceptible tumour targets), spleen and bone marrow cellularity, leukocyte and thrombocyte counts in peripheral blood, serum levels of selected pro- and anti-inflammatory cytokines, and development of the induced tumour nodules in the lungs.
The obtained results will broaden our understanding of bio-medical outcomes of internal contamination with tritium by furnishing evidence of its possible pro- or anti-neoplastic and/or pro- and anti-inflammatory effects.

THRESHOLD DOSES OF SINGLE OR FRACTIONATED X-RAYS FOR STIMULATION OF NATURAL ANTI-NEOPLASTIC CELLS IN MICE

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Although tumour-inhibitory effects of low-level exposures to ionizing radiation have been demonstrated, the range of the doses capable of reproducibly triggering anti-neoplastic functions of the immune cells is virtually unknown. The aim of the present study was to estimate threshold doses of single or fractionated irradiations with X-rays for stimulation of the natural killer-type and macrophage-mediated anti-tumour activities in mice.

Peritoneal macrphages (Mφ) and NK cell-enriched splenoctes (NK cells) were collected from BALB/c mice exposed to single or fractionated total doses of X-rays equal to 0.01, 0.02, 0.03, 0.04, 0.05, 0.07, 0.1, 0.2, 0.3, 0.4, 0.5, 1.0, 2.0, 3.0, 4.0, or 5.0 Gy. Then, cytotoxic activity of NK cells and production of nitric oxide (NO) by Mφ were assayed. Mice irradiated with total doses of 0.1, 0.2, 0.5 or 1.0 Gy were intravenously injected with L1 sarcoma cells two hours after the exposures. Fourteen days later the developed tumour colonies were counted on the lungs' surface.

All but 0.5 Gy single and fractionated irradiations with total doses from 0.03 to 2.0 Gy X-rays significantly enhanced cytotoxic activities of NK cells. Production of NO by Mφ was significantly stimulated by single or fractionated exposures to up to 2.0 Gy total doses. Single irradiations with 0.1 or 0.2 Gy, but not with 0.5 or 1.0 Gy, and fractionated irradiations with total doses of 0.1, 0.2, or 1.0 Gy significantly reduced the development of the induced pulmonary tumor colonies in the exposed mice.

The results suggest that the upper threshold for the stimulation by a single irradiation with X-rays of the selected anti-tumour reactions of NK lymphocytes and cytotoxic macrophages approximates 0.4 Gy whereas for the fractionated irradiations the threshold can be set between 1.0 and 2.0 Gy total doses (0.1-0.2 Gy per fraction).

LOW-DOSE GAMMA IRRADIATION INHIBITS IL-6 SECRETION FROM FIBROBLASTS THAT PROMOTES HBEC TRANSFORMATION BY CIGARETTE SMOKE

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Despite decades of research in defining the health effects of low-dose (<100 mGy) ionizing photon radiation (LDR), the relationship between LDR and human cancer risk remains elusive. Because chemical carcinogens modify the tumor microenvironment which is critical for cancer development, we investigated the role and mechanism of LDR in modulating the response of stromal cells to chemical carcinogen-induced lung cancer development. Secretion of proinflammatory cytokines IL-6, CXCL1 and CXCL5 from human lung fibroblasts was induced by cigarette smoke carcinogen benzo[a]pyrene diol epoxide (BPDE) which in turn was inhibited by a single dose of LDR. The activation of NF-κB, which is important for BPDE-induced IL-6 secretion, was effectively suppressed by LDR. In addition, conditioned media from BPDE-treated fibroblasts activated STAT3 in immortalized normal human bronchial epithelial cell line Beas-2B, which was blocked with an IL-6 neutralizing antibody, while conditioned medium from LDR-primed and BPDE-treated fibroblast showed diminished capacity in activating STAT3. Finally, IL-6 enhanced BPDE-induced Beas-2B cell transformation in vitro. Together these results suggest that LDR may inhibit cigarette smoke-induced lung carcinogenesis through suppressing secretion of cytokines such as IL-6 from fibroblasts in lung tumor microenvironment.

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NON-TARGETED RADIATION EFFECTS WITH HIGH DOSE RATE (HDR) BRACHYTHERAPY

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Radiation-induced bystander effects (RIBEs) occur when unirradiated cells in close proximity to directly irradiated cells behave as if they were similarly exposed to radiation. Such an effect has been studied extensively at the lower dose level. However, the high dose regime, often required for therapeutic radiation treatments, requires further study. In the present study, a colony-forming *in vivo* assay was used for the detection of non-targeted effects. Samples of blood, urine, and biopsies were collected from 15 oesophageal carcinoma patients undergoing fractionated high dose rate (HDR) intraluminal brachytherapy (ILBT). For this study, ethics approval was obtained from the HHS/FHS research ethics board. Follow-up blood and urine samples were subsequently collected 3 weeks after the final fraction, in order to observe whether a bystander signalling mechanism remains. HPV-G keratinocytes, a thoroughly tested reporter cell line, was used for the assays. Our data shows evidence of increase cell proliferation and death, for both blood and urine samples, when patients underwent HDR-ILBT. The blood results coincide with out-of-field bystander effects found within the literature, such as clastogenic effects. Tissue explants excised from the esophageal mucosa, after 3 fractions of HDR-ILBT, show no evidence of a bystander signal relative to controls. Very little change is observed in cell survival at the start and end of the fractionated regimen for the explants. This result may be attributed to the radioresistant phenotypes typically seen with esophageal carcinomas. Unfortunately, there is considerable interpatient variability in this study, most likely due to genetic and lifestyle factors, which makes it quite difficult to detect a definitive pattern at this time. Additionally, amongst the 3 samples collected from the same individual, results do not yet indicate a clear trend. Future work will look into each patient's therapeutic outcome following a complete HDR-ILBT regimen, and an appropriate statistical analysis will be performed in an attempt to reveal any underlying correlates that may exist.

BIPHASIC DOSE RESPONSES TO PHYTOESTROGENS: AN EVALUATION OF MECHANISMS

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Phytoestrogens are plant-derived chemical constituents with estrogen mimetic effects. Phytoestrogens can include flavonols such as kaempferol and quercetin, coumestans such as coumestrol, and isoflavones such as genistein and daidzein. These compounds are often found in food sources such as soya bean and, as such, are relevant to human nutrition and health. Phytoestrogens have been noted to exert beneficial effects on various diseases such as breast cancer, but their efficacy and safety are disputed. Evidence suggests that phytoestrogens have complex dose response relationships that may be an example of hormesis. Hormesis is defined as a dose response model characterized by low dose stimulation and high dose inhibition, manifesting as a nonlinear j-shaped or inverted-u-shaped dose response curve. This work seeks to evaluate the mechanisms behind the biphasic dose responses of isoflavones and select other phytoestrogens in gene expression and cell proliferation.