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IMPLICATIONS FOR TOXICOLOGY, MEDICINE AND RISK ASSESSMENT

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ABSTRACT BOOK

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TABLE OF CONTENTS

CLINICAL / THERAPEUTIC SESSION

MECHANISMS AND EXAMPLES OF BIPHASIC DOSE RESPONSE IN LOW-LEVEL LIGHT THERAPY

Ying-Ying Huang, Wellman Center for Photomedicine, Massachusetts General Hospital, Boston MA, Wellman Center for Photomedicine, Massachusetts General Hospital, Boston MA, Aesthetic Plastic Laser Center, Guangxi Medical University, Nanning, Guangxi, P. R China
Sulbha K Sharma, Wellman Center for Photomedicine, Massachusetts General Hospital, Boston MA, Department of Dermatology, Harvard Medical School, Boston MA
Gitika B Kharkwal, Wellman Center for Photomedicine, Massachusetts General Hospital, Boston MA, Department of Dermatology, Harvard Medical School, Boston MA
Luis De Taboada, PhotoThera Inc, Carlsbad, CA
Thomas McCarthy, PhotoThera Inc, Carlsbad, CA
Michael R Hamblin, Wellman Center for Photomedicine, Massachusetts General Hospital, Boston MA, Department of Dermatology, Harvard Medical School, Boston MA, Harvard-MIT Division of Health Sciences and Technology, Cambridge MA

HORMESIS-BASED ANTI-AGING PRODUCTS: A CASE STUDY OF A NEW COSMETIC

Suresh Rattan, University of Aarhus, Denmark

THERAPEUTIC IMPLICATIONS OF HORMESIS

Wayne Jonas, Samueli Institute, Alexandria VA

THE SANDPILE MODEL: OPTIMAL STRESS, COMPLEXITY, AND HORMESIS

Martha Stark, MD, Harvard Medical School, Newton MA

SURGICAL STRESS AND THE HEAT SHOCK RESPONSE: MODELS OF STRESS CONDITIONING

George A Perdrizet, Wound Care and Hyperbaric Medicine, Kent Hospital, Warwick, RI
Lawrence Hightower, University of Connecticut, Storrs, CT
Cassandra Godman, University of Connecticut, Storrs, CT
Charles Giardina, University of Connecticut, Storrs, CT

MECHANISMS AND EXAMPLES OF BIPHASIC DOSE RESPONSE IN LOW-LEVEL LIGHT THERAPY

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Low-level light (laser) therapy (LLLT) has been used for over forty years, yet the basic mechanisms that underlie its beneficial effects remain incompletely understood. The incident photons are thought to be absorbed by chromophores such as cytochrome c oxidase located in the mitochondria of cells, and cellular respiration and ATP levels are increased after LLLT. At the same time levels of reactive oxygen species (ROS) and nitric oxide (NO) are increased and it is believed that these species are responsible for the activation of cell signaling pathways and changes in gene transcription. The beneficial changes observed after LLLT tend to be lost if the dose of light is increased, and if the amount of light is increased even further, actual adverse effects may ensue. This can now be explained in cell biology terms as two distinct peaks of ROS production and NO release have been observed. The first peak occurs between fluences of 0.3-3J J/cm^2 and the second peak occurs between fluences of 3-100 J/cm^2. We propose that the first peak of ROS and NO is associated with positive signaling events triggered by activation of transcription factors such as nuclear factor kappa B that is responsive to ROS, and the second larger peak of ROS and NO is associated with mitochondrial damage and cellular apoptosis. Numerous real life examples of the biphasic dose response in LLLT will be presented.

HORMESIS-BASED ANTI-AGING PRODUCTS: A CASE STUDY OF A NEW COSMETIC

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Application of hormesis in aging research and interventions is becoming increasingly attractive and successful. The reason for this is the realization from extensive biogerontological research that aging occurs mainly due to the failure of maintenance and repair pathways, which comprise the so-called homeodynamic space of the biological systems. Progressive shrinkage of the homeodynamic space due to the occurrence and accumulation of macromolecular damage is the molecular basis of aging. Mild stress-induced activation of one or more stress response pathways, and its consequent stimulation of repair mechanisms, has been shown to be effective in reducing the accumulation of molecular damage. For example, since 1998, we have shown that repeated mild heat stress has anti-aging effects on growth and various other cellular and biochemical characteristics of normal human skin fibroblasts, keratinocytes and endothelial cells undergoing aging *in vitro.* Therefore, searching for potential hormetins – conditions and compounds eliciting stress response-mediated hormesis – is drawing attention of not only the researchers but also the industry involved in developing healthcare products, including nutriceuticals, functional foods and cosmeceuticals. One of the first successful product development based in the ideas of hormesis is a skin care cosmetic product by a French company, Givenchy. Extensive experiments performed to analyse the gene expression at the level of mRNAs and proteins show that the active ingredient derived from the plant Sanchi *(Panax notoginseng)* is an inducer of stress proteins, especially the heat shock protein Hsp70, in human skin cells. That this compound also has significant positive effects against facial wrinkles and other symptoms of facial skin aging as tested clinically, is an evidence for stress-induced hormesis being applicable to human beings.

THERAPEUTIC IMPLICATIONS OF HORMESIS

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The idea that low-dose adaptive effects as described in hormesis can be used clinically has been discussed for hundreds years. Paracelsus famous adage that "the dose makes the poison" and the common folk saying that one can be cured by "the hair of the dog that bit you", and the non-mainstream system of homeopathy speak to this idea. So why has so little research been done on the possible clinical utility of hormesis? Can a field of therapeutic hormesis be scientifically developed? What areas of clinical hormesis seem to be the most promising to explore? This presentation will explore these concepts and proposes some initial areas or research where the utility of hormesis might be investigated.

THE SANDPILE MODEL: OPTIMAL STRESS, COMPLEXITY, AND HORMESIS

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The sandpile model (developed by chaos theorists) is an elegant visual metaphor for the cumulative impact of environmental stressors on complex adaptive systems -- an impact that is paradoxical by virtue of the fact that the grains of sand being steadily added to the gradually evolving sandpile are the occasion for both its disruption and its repair. In other words, not only do the grains of sand being added precipitate partial collapse of the sandpile but they become the means by which the sandpile is able to build itself back up -- each time at a new homeostatic set point. So too the body is continuously refashioning itself at ever higher levels of complexity and integration -- not just *in spite of* "stressful" input from the outside but *by way of* that input.

Based upon study of the nonlinear dynamics characterizing a sandpile's evolution, the claim will be made that -- whatever the agent tested ("poison" or "medication"), whatever the endpoint measured ("health-promoting" or "disease-promoting"), and biochemical individuality notwithstanding -- three distinct phases inevitably emerge along the (hormetic) dose-response curve: (1) "minimal load" (a loading stage during which the system's homeostatic mechanisms allow it to preserve both its status quo and its level of complexity); (2) "optimal load" (a compensatory stage during which the system's underlying resilience enables it to evolve to ever higher levels of complexity as it advances through iterative cycles of defensive collapse -- a "minor avalanche" in chaos theory -- and adaptive reconstitution); and (3) "overload" (a stage of decompensation during which the overburdened system sustains catastrophic collapse -- a "major avalanche" in chaos theory -- and devolves to a much lower level of complexity).

In essence, too much stress -- "traumatic stress" -- will be too overwhelming for the system to process and integrate, triggering instead devastating breakdown. Too little stress will provide too little impetus for transformation and growth, serving instead simply to reinforce the system's status quo. But just the right amount of stress -- "optimal stress" -- will "provoke" recovery by jumpstarting the system's innate capacity to heal itself.

Keywords: sandpile model, complexity theory, hormesis, stress response

SURGICAL STRESS AND THE HEAT SHOCK RESPONSE: MODELS OF STRESS CONDITIONING

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The ability of cellular and multi-cellular organisms to adapt to unfavorable environmental conditions has been extensively studied and reported for as long as biology has been a science. Cellular life forms have evolved to sense, process and respond to the immediate physical state of its surroundings. Survival is often determined by which individual can most efficiently and adequately adapt to a change in its physical environment. The family of stress genes (a.k.a., heat shock genes) is recognized as one set of fundamental genes which play a dominant role in cellular adaptation to adverse events and conditions. Through evolution, oxidant stress has been and remains a fundamental cellular toxin against which all forms of life must defend. Modern medical therapies have created artificial conditions in which the degree and duration of exposure to oxidant stress commonly reaches extreme levels, often times with unwanted detrimental effects for human life and limb. Modern medical treatments purposely expose patients to oxidant stresses such as acute inflammation, hypoxia, and ischemia-reperfusion events. Paradoxically, another oxidant stressor, hyperbaric oxygen, can be used to ameliorate these patho-physiologic oxidant stresses and assist tissues in recovery. Exposure of uninjured, normal tissues in their baseline state to hyperoxia has the ability to initiate the cellular changes which may help to resist injury from acute inflammation, hypoxia and ischemia-reperfusion events. This increased resistance is associated with enhanced expression of stress genes, which act as "molecular chaperones" to stabilize intracellular proteins. The historical, cellular and physiologic basis for preconditioning protocols will be presented and a relationship to clinical preconditioning using hyperbaric oxygen will be addressed.

PLENARY SESSION

CENTRAL ROLE OF THE BRAIN IN STRESS AND ADAPTATION: ALLOSTASIS AND ALLOSTATIC LOAD

Bruce McEwen, The Rockefeller University, New York, NY

CENTRAL ROLE OF THE BRAIN IN STRESS AND ADAPTATION: ALLOSTASIS AND ALLOSTATIC LOAD

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The brain is the central organ of stress because it interprets what is stressful and also determines behavioral and physiological responses. Besides major life events, the aggravations of daily life elevate activities of physiological systems so as to cause some measure of wear and tear. We call this "allostatic load", and it reflects not only the impact of life experiences but also of genes; individual life-style habits reflecting items such as sleep quality and quantity; diet, exercise and substance abuse; adverse early life experiences that set life-long patterns of behavior and physiological reactivity; and exposure to toxic agents in the environment. Hormones associated with stress and allostatic load protect the body in the short-run and promote adaptation ("allostasis"), but in the long run overuse and dysregulation of allostasis causes changes in the body and brain that lead to disease ("allostatic load"). Mediators of allostasis include autonomic nervous system activity, glucocorticoids and pro- and anti-inflammatory cytokines and these operate as a non-linear network, with each mediator capable of biphasic effects and regulating the other mediator systems. The brain is a target of stress and stress and stress hormones produce both adaptive and maladaptive effects on the brain throughout the life course. The amygdala is important in fear and strong emotions and the prefrontal cortex is involved in attention, executive function and working memory while hippocampus mediates spatial and episodic memory. Hippocampal and medial prefrontal cortical neuron dendrites become shorter and less branched and dentate gyrus neurogenesis is suppressed by repeated stress, whereas amygdala and orbitoprefrontal cortical neurons show hypertrophy after repeated stress. Repeated stress as well as circadian disruption, as in jet lag and shift work, promote structural remodeling of brain circuits and impair cognitive function as well as causing systemic allostatic load.

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ENVIRONMENTAL SESSION

HORMETIC RESPONSES OF THE AQUATIC INVERTEBRATE *DAPHNIA MAGNA* TO EXPOSURE TO ENERGETIC COMPOUNDS

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XENOHORMETIC, HORMETIC, AND CYTOSTATIC SELECTIVE FORCES DRIVE THE EVOLUTION OF LONGEVITY REGULATION MECHANISMS WITHIN ECOSYSTEMS

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ISSUES IN THE INTERPRETATION OF LOW DOSE EFFECTS IN RADIOBIOLOGY AND ENVIRONMENTAL RADIATION PROTECTION

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BYSTANDER EFFECTS AND ADAPTIVE RESPONSES MODULATE THE BIOLOGICAL RESPONSES TO LOW DOSE IONIZING RADIATION

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DEBUNKING THE MYTH OF INCREASED CANCER INCIDENCE ATTRIBUTED TO MEDICAL RADIATION

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HUMAN HEALTH AND THE BIOLOGICAL EFFECTS OF LOW DOSE TRITIUM IN DRINKING WATER

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PUBLIC POLICY AND HORMESIS

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HORMETIC RESPONSES OF THE AQUATIC INVERTEBRATE *DAPHNIA MAGNA* TO EXPOSURE TO ENERGETIC COMPOUNDS

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In order to, in the future, facilitate more accurate predictions of organismal responses to exposure to low concentrations of military energetics, the purpose of the present study was to identify the concentration range in which hormetic responses are observed for representatives of three different classes of energetic compounds using the model aquatic invertebrate *Daphnia magna* in 21-day bioassays. The energetics assessed included hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX), trinitrotoluene (TNT), and a newly developed nitrogen-rich tetrazole energetic triaminoguanidinium 1-methyl-5-nitriminotetrazolate (TAGMNT). Observed hormetic responses included increases in *D. magna* reproduction at TNT concentrations ranging from 0.06 to 0.22 mg/L and increases in *D. magna* growth (as measured by length) at TNT concentrations ranging from 0.004 to 0.97 mg/L. Apparent, yet non-significant, increases in *D. magna* reproduction and growth were observed at RDX concentrations ranging from 0.02 mg/L to 14 mg/L and in growth of *D. magna* exposed to TAGMNT at concentrations ranging from 0.2 to 10 µg/L. Ongoing efforts include further testing to confirm the hormetic range for these compounds and initial attempts to begin elucidating the mechanism of the observed hormetic responses in *D. magna* using gene microarrays.

XENOHORMETIC, HORMETIC, AND CYTOSTATIC SELECTIVE FORCES DRIVE THE EVOLUTION OF LONGEVITY REGULATION MECHANISMS WITHIN ECOSYSTEMS

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We recently found that lithocholic acid, a bile acid, extends yeast longevity. Unlike mammals, yeast do not synthesize bile acids. We therefore hypothesize that bile acids released into the environment by mammals may act as interspecies chemical signals providing longevity benefits to yeast. In our hypothesis, these mildly toxic compounds released into the environment by mammals may create selective pressure for the evolution of yeast species that can respond to the resulting mild cellular damage by developing the most efficient stress protective mechanisms. By fusing the xenohormesis hypothesis [Cell (2008) 133:387-391], the anti-aging side effect hypothesis [Aging (2009) 1:511-514], and our hypothesis on longevity regulation by bile acids within ecosystems, we put forward a unified hypothesis of the xenohormetic, hormetic, and cytostatic selective forces driving the evolution of longevity regulation mechanisms at the ecosystemic level. In our unified hypothesis, organisms from all domains of life within an ecosystem are able to synthesize chemical compounds that 1) are produced and then released into the environment permanently or only in response to deteriorating environmental conditions, increased population density of competitors and/or predators, or changes in food availability and its nutrient and/or caloric content; 2) are mildly toxic compounds that trigger a hormetic response in an organism that senses them or, alternatively, are not toxic for any organism within the ecosystem and do not cause a hormetic response; 3) are cytostatic compounds that attenuate the TOR-governed signaling network (*e.g.*, rapamycin and resveratrol) or, alternatively, do not modulate this growth-promoting network (*e.g.*, bile acids) and 4) extend longevity of organisms that can sense these compounds, thereby increasing their chances of survival and creating selective force aimed at maintaining the ability of organisms composing the ecosystem to

respond to these compounds by undergoing specific life-extending changes to their physiology.

ISSUES IN THE INTERPRETATION OF LOW DOSE EFFECTS IN RADIOBIOLOGY AND ENVIRONMENTAL RADIATION PROTECTION

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The last 15 years have seen a major paradigm shift in radiation biology. Several discoveries challenge the DNA centric view which holds that DNA damage is the critical effect of radiation irrespective of dose. This theory leads to the assumption that dose and effect are simply linked – the more energy deposition, the more DNA damage and the greater the biological effect. This is embodied in radiation protection (RP) regulations as the linear-non-threshold or LNT model. However the science underlying the LNT model is being challenged particularly in relation to the environment because it is now clear that at low doses of concern in RP, cells, tissues and organisms respond to radiation by inducing responses which are not predictable by dose. These include adaptive responses, bystander effects, genomic instability and low dose hypersensitivity/induced radioresistance and are commonly described as *stress* responses, while recognizing that "stress" can be good as well as bad. The phenomena contribute to observed radiation responses and appear to be influenced by genetic, epigenetic and environmental factors, meaning that dose and response are not simply related. The big question is whether our discovery of these phenomena means that we need to re-evaluate RP approaches. This is the subject of presentation. The so called "non-targeted" mechanisms mean that low dose radiobiology is very complex and supra linear or hormetic responses are equally probable but their occurrence is unpredictable for a given individual. Issues which may need consideration are synergistic or antagonistic effects of other pollutants because RP at present only looks at radiation dose but the new radiobiology means that chemical or physical pollutants which interfere with tissue responses to low doses of radiation could critically modulate the predicted risk. Similarly, the "health" of the organism could determine the effect of a given low dose by enabling or disabling a critical response. These issues will be discussed.

BYSTANDER EFFECTS AND ADAPTIVE RESPONSES MODULATE THE BIOLOGICAL RESPONSES TO LOW DOSE IONIZING RADIATION

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The health risks of low level radiation have been the subject of intense debate. To reduce the uncertainty in evaluating these risks, research advances in cellular and molecular biology are being used to characterize the biological effects of low dose radiation exposures and their underlying mechanisms. Radiation type, dose rate, genetic susceptibility, cellular metabolic state, growth stage, levels of biological organization and environmental parameters are among the factors that modulate interactions among signaling processes that determine the outcome of low dose exposures. Whereas, recommended radiation protection guidelines assume a linear dose-response relationship in estimating radiation cancer risk, investigation of phenomena such as adaptive responses and bystander effects suggest that low dose/low fluence-induced signaling events act to alter linearity of the dose-response relation as predicted by the biophysical argument.

Using normal human or rodent cells maintained in culture and a variety of biological endpoints, we have shown that exposure to low dose from ^{137}Cs, ^{60}Co γ-rays or energetic protons triggers signaling events that protect cells from endogenous oxidative damage or damage due to a subsequent challenge dose of ionizing radiation. DNA repair, oxidative metabolism and cell cycle checkpoints are implicated in the biological responses observed, and involve differential regulation of signaling processes, including epigenetic events, in low or high dose irradiated cells. Moreover, the induced adaptive effects were communicated to neighboring non-targeted cells and protected the latter against stress from a subsequent exposure to radiation. Using mice, we have shown that mitochondria, which are active participants in oxidative metabolism, play a crucial role in the induced adaptive responses, which appear to be transient and tissue-dependent.

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DEBUNKING THE MYTH OF INCREASED CANCER INCIDENCE ATTRIBUTED TO MEDICAL RADIATION

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Recent publications have raised concerns about the increasing medical radiation dose to the public and the implied enhanced cancer risk, based on a linear non-threshold (LNT) extrapolation of high-dose data. Considerable efforts are underway to reduce the medical radiation dose to the public. The purpose of this work is to estimate the impact of medical radiation dose on cancer incidence in the US population to see if the concerns regarding the medical radiation dose are justified. A simplified model is used to estimate the medical radiation attributable increase in cancer incidence in the US population with the following assumptions: The per capita medical radiation dose is assumed to increase from 0.41 mSv in 1965 to 0.54 mSv in 1980 and to 3.1 mSv in 2006, with a linear interpolation between the years. LNT extrapolation and an exponential lag time model are assumed for estimating the cancer risk from radiation. The model calculation shows that as much as 0.5% of cancers in 1992 and 1.5% of cancers in 2007 in USA could be attributed to past medical radiation. In contrast, the age-adjusted cancer incidence rate (compiled by SEER, for example) has decreased by ~7% between these years, indicating that medical radiation may be an insignificant factor in the observed changes in cancer rates or that the underlying LNT assumption may not be valid. In addition, since there has been ~1.4% year-to-year variation in the observed (SEER) cancer incidence rates, it may not be feasible to detect the predicted ~1% increase in cancers attributable to medical radiation between these years. Reasonable excursions of the model assumptions do not alter these conclusions. In view of the above, the tremendous efforts currently underway to reduce medical radiation dose may not result in any (measurable) health benefit, and should be reconsidered.

HUMAN HEALTH AND THE BIOLOGICAL EFFECTS OF LOW DOSE TRITIUM IN DRINKING WATER

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The Ontario Drinking Water Advisory Council (ODWAC) issued a formal report in May 2009, in response to a request by the Minister of the Environment, concluding that the Ontario Drinking Water Quality Standard for tritium should be revised from the current 7000 Bq/L level to a new lower 20 Bq/L. In response to this recommendation, an international scientific symposium was held at McMaster University to address the issues surrounding this change in direction and the validity of a new policy. The new proposed standard would set a drinking water annual radiation dose annual limit of 0.0003 mSv, about three times higher dose than from tritium naturally occurring in drinking water. This new standard is in direct contrast with national and international standards for safe levels of radiation exposure which is set at 1 mSv/year for the general public. Scientific research from leading authorities concerning the carcinogenic health effects of tritium exposure support the notion that the current standard of 7000 Bq/L (annual dose of 1.0 mSv) is a safe standard for human health and additional manmade radiation exposure levels. There has been no cost benefit analysis for human health regarding this new recommendation so the actual impact on society (cost of energy production) is unknown. It was concluded that the new recommendation is not supported by any new scientific insight about negative consequences of low dose effects, it may be contrary to new data on potential benefits of low dose effects, and given the lack of cost versus benefit analysis it is unknown what the total impact on society would be by such a dramatic policy change.

PUBLIC POLICY AND HORMESIS

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Hormesis encounters problems in terms of public policy partly because of issues of boundaries, and partly because of simplistic definitions,

After 9/11 the western world became more polarized. Right or wrong, good or bad – a large number of simplistic assumptions were made. Intrinsic to the process was that criticism of the decision makers could be equated with support for those with opposing views. The idea of constructive criticism disappeared from the public discourse. By eliminating dissenting voices, non-truthful ideas could be perpetuated. Even today a majority of the population do not realize there has never been any discernable link between Al Quaeda and the then Iraqi administration. In effect, truth became the first casualty of the 9/11 events.

Nuanced truth also became a casualty. It is easier to polarize and subsequently demonise a group, making all actions of that group bad, rather than dissecting out the spectrum of events that ultimately led to 9/11.

A direct consequence of 9/11 was the erection of boundaries round societies – strenuous efforts were made to keep the "other" out. The porosity of these boundaries was decreased, again through politicians trying to show how tough they were on crime/terrorism. Again, criticism of those policies was equated with being soft on crime/terrorism.

One conceptual difficulty of this approach is that no new ideas or knowledge can pass through a non-porous boundary. It is not conducive to a balanced, nuanced approach.

The entire concept of hormesis requires a balanced, thinking approach. It also requires an individualized approach, allowing an entire spectrum of response rather than either/or.

The individual needs the self-knowledge to know themselves. I may know two alcoholic beverages are good for me, but I cannot presume that knowledge for another. I think it is this switching from good effects(two drinks) to bad effects (ten drinks) and the need for self-knowledge and therefore personal responsibility that makes politicians wary of hormesis. Politicians presume to know what is best for us, collectively. Politicians like to control, and do not like allowing personal responsibility.

Hormesis does not allow for simplistic regulation, and so I would argue that any real change in public policy must come from public demand following public education.

BIOMEDICAL SESSION

HORMESIS CHALLENGES PHARMACEUTICAL INDUSTRY RESEARCH AND DEVELOPMENT: SOLUTIONS FROM A REGULATORY PERSPECTIVE
Kenneth I. Maynard, Sanofi-aventis, US, Inc, Bridgewater, NJ

COMMUNICATING HEALTH RESEARCH TO THE PUBLIC: THE CHALLENGE OF PROMOTING HEALTH IN A U-SHAPED WORLD
David J. Waters, Purdue University, West Lafayette, IN

DIETARY RESTRICTION, ACUTE STRESS RESISTANCE AND HORMESIS
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HORMESIS-BASED DEVELOPMENT OF BOTANICAL INSECT ANTIFEEDANTS AS THERAPEUTIC AGENTS
Mark Mattson, National Institute on Aging Intramural Research Program, Baltimore, MD

OXIDATIVE DAMAGE: IS DAMAGE THE CORRECT TERM?
Radak Zsolt, Semmelweis University, Budapest, Hungary

MOLECULAR SIGNATURES OF ADAPTIVE STRESS RESPONSES: STUDYING MOLECULAR MECHANISMS OF ADAPTATION
Ignacio Rubio, Friedrich-Schiller-University Jena, Jena, Germany

UNDERSTANDING THE BENEFICIAL EFFECTS OF PHARMACOLOGICAL SIRT1 ACTIVATION
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SIMULATION STUDIES TO COMPLEMENT OBSERVATIONAL DATA: WHAT CAN WE LEARN? HOW SHOULD THEY BE USED?
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HORMESIS CHALLENGES PHARMACEUTICAL INDUSTRY RESEARCH AND DEVELOPMENT: SOLUTIONS FROM A REGULATORY PERSPECTIVE

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Traditionally, hormesis was confined primarily to the fields of toxicology, radiation biology and biochemistry. The literature explosion surrounding hormesis over the past 15 years, however, extends the application of biphasic dose-response curves across many areas of biomedical science and clinical medicine. This work, at least in part, reveals challenges for identifying a dose with the optimal risk/benefit ratio for research and development (R&D) in the pharmaceutical industry. This presentation will address these points and provide solutions to the R&D challenges based upon considerations in obtaining dose-response information and clinical trials designs.

COMMUNICATING HEALTH RESEARCH TO THE PUBLIC: THE CHALLENGE OF PROMOTING HEALTH IN A U-SHAPED WORLD

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The perception that is pervasive among the public is that, when it comes to taking dietary supplements, more is better. A growing body of scientific evidence, however, suggests that the dose response between DNA damage and the dietary intake of nutrients, such as selenium, zinc and beta-carotene, is in fact U-shaped. Therefore more of these "good things" may not necessarily be a good thing. This concept is especially relevant to health-conscious men and women, who are ironically at highest risk for the ill-effects of oversupplementation because they are already consuming high-quality diets rich in vitamins and minerals. Now, more than ever, we need a new approach to cancer prevention – one that is personalized. We define personalized cancer prevention as a strategy that will enable each person to reduce his or her risk for lethal cancer by matching the dose, duration, and timing of an intervention with their own cancer risk profile (*Waters at al, Nutrition and Cancer 2008; 60:1-6*). Defining the U-shaped relationship between DNA damage and cancer-modulating nutrients moves us one step closer to developing personalized, cancer-reducing interventions. It follows from this understanding that not all individuals will necessarily benefit from increasing their nutrient intake. The deep-rooted metaphor "more is better" is a significant obstacle to our efforts to successfully communicate the good things that really do promote health *(Waters and Chiang, ETC: A Review in General Semantics 2010; 67:218-226*). Because a single recommendation for everyone is plainly inadequate, high priority should be placed on developing young scientists who have skills in communicating health research to the public.

DIETARY RESTRICTION, ACUTE STRESS RESISTANCE AND HORMESIS

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Dietary restriction, defined as reduced food intake without malnutrition, extends lifespan, improves metabolic fitness and increases stress resistance in most organisms tested. However, the underlying nutritional triggers and genetic requirements of these benefits remain elusive, particularly in mammals. Previously we reported that short-term dietary restriction as well as fasting increase resistance to the acute stress of renal ischemia reperfusion injury, a phenomenon we call dietary preconditioning. Here we examined the nutritional and genetic basis of dietary preconditioning. We found that total protein deprivation for 6-14 days in the absence of reduced calorie intake led to increased resistance to renal ischemia reperfusion injury. Deprivation of individual essential amino acids including tryptophan, methionine and leucine, as well as pharmacological activation of the amino acid starvation response, also improved outcome following ischemic kidney injury. The role of amino acid sensing in stress resistance was tested using mice deficient in the amino acid deprivation sensor Gcn2. Together, our data point to amino acid sensing as a key modulator of stress resistance by dietary preconditioning. Implications for the role of hormesis in stress resistance and longevity induced by dietary restriction will be discussed.

HORMESIS-BASED DEVELOPMENT OF BOTANICAL INSECT ANTIFEEDANTS AS THERAPEUTIC AGENTS

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We are testing the hypothesis that some of the chemicals that are concentrated in exposed regions of plants and their fruits are beneficial for health because they are toxins; such "botanical pesticides" (BP) function to dissuade insects and other organisms from eating the plants. Hundreds of BP have been isolated from various plants using insect anti-feedant bioassays. We reasoned that when consumed in subtoxic doses BP may activate adaptive cellular stress response pathways and thereby increase the resistance of cells and organisms to disease. To test this hypothesis we developed cell culture screens to identify BP that activate adaptive stress response pathways at doses that do not harm the cells. Given our interest in the brain and neurodegenerative disorders we transfected human neuronal cells with reporter gene constructs for the Nrf2 – ARE, NF-κB or FOXO pathways which are known to induce the expression of genes encoding antioxidant and phase 2 detoxification enzymes and protein chaperones. Fifty different BP, representing a range of structural categories, were screened in dose response experiments in which both reporter gene activation and cell viability were quantified. Many of the BP exhibited biphasic dose responses. Particularly notable was plumbagin, a small molecule with a structure similar to menadione, which strongly activated the Nrf2 – ARE pathway and induced the expression of the antioxidant enzymes heme oxygenase 1 and NQO1. Plumbagin protected neurons in cell culture and mouse models of ischemic stroke. Plumbagin also activated a homologous adaptive stress response pathway and increased the lifespan of the nematode *C. Elegans*. A series of plumbagin analogs was synthesized and screened, with one of the analogs exhibiting a dose response profile superior to plumbagin. Our findings suggest a potential for hormesis-based drug discovery based on screening BP in human cells and animal models.

OXIDATIVE DAMAGE: IS DAMAGE THE CORRECT TERM?

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Reactive oxygen and nitrogen species (RONS) are continuously challenging the body and because of their reactivity, their presence is often judged by stable products, called oxidative damage markers. However, it is interesting to note, that the levels of oxidative damage markers, such as malondyaldehyde, protein carbonyl groups or 8-oxoG, cannot be completely eliminated even with massive amounts of antioxidants or over expression of antioxidant enzymes. Therefore, it can be suggested that a certain level of so called oxidative damage is necessary for cells, and can work as a signaling process for vital functions. The accumulation of carbonyl groups is an accepted, well documented process as a result of aging. However, histone carbonylation decreases in old animals, probably providing better chromatin structure to decrease the extensive damage to DNA. Under certain conditions, 8-oxoG might be less harmful to DNA, especially at the non-coding section, so that the cleaved form could induce inflammation. Needless to say, oxidative damage over a certain level is jeopardizing the viability of organisms.

Physical exercise is known to be an inducer (acute bout of exercise) and suppressor (regular exercise) of oxidative cellular damage, and systemic adaptation can result in increased mean-life span. Interestingly, regular exercise does not always decrease the levels of RONS in the cellular milieu but increases the resistance to oxidative stress and modulates oxidative damage-associated signaling pathways.

MOLECULAR SIGNATURES OF ADAPTIVE STRESS RESPONSES; STUDYING MOLECULAR MECHANISMS OF ADAPTATION

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On behalf of all members of the research training group Molecular Signatures of Adaptive Stress Responses

"All things are poison and nothing is without poison, only the dose permits something not to be poisonous" - the magic dictum of Paracelsus is of formidable relevance in medicine and biology. Organisms are constantly faced with noxious insults to which they can react with a whole spectrum of responses in dependency of the quality of the stressor and a variety of predisposition factors. For example, cells and organisms can react to environmental insults with injury and degeneration or on the contrary they can acquire stress resistance and consequently lead a healthier life, as anticipated by Nietzsche 1888 in his classic quote “What does not kill me makes me stronger”. How do stressors strengthen cells and organisms? What factors predispose a biological entity to move in either direction in response to environmental insults? An interdisciplinary graduate research platform entitled *Molecular Signatures of Adaptive Stress Responses,* composed of 15 research laboratories from academia and independent research institutions in the city of Jena, Germany, will be devoted to deciphering the mechanisms that underlie the adaptation to biological and physical stressors. In my presentation I will provide an overview of the topics covered by this research conglomerate which range from mitohormesis to adaption mechanisms downstream of osmotic stress or DNA damage.

UNDERSTANDING THE BENEFICIAL EFFECTS OF PHARMACOLOGICAL SIRT1 ACTIVATION

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Sirtuins, a family of NAD^+-dependent deacetylases, promote survival and mediate beneficial effects of caloric restriction in multiple species. Overexpression of SIRT1 in mice improves metabolic function, suppresses cancers, and delays atherogenesis, among other health benefits. Human genetics studies also support a role for SIRT1 in maintaining human health status with age. Increasing SIRT1 activity could therefore potentially provide significant benefits to society. Small molecule activators of SIRT1, such as resveratrol and SRT1720, improve multiple health parameters in mice,, including atherosclerosis, fatty liver, hyperglycemia, and endurance. In inbred strains of mice, germline knockout of SIRT1 is embryonic lethal. Outbred knockout mice are unresponsive to some of the beneficial effects of caloric restriction and resveratrol, but are also small, sterile, and suffer from developmental abnormalities. Therefore a better system is needed to avoid the developmental defects of SIRT1 germline knockout. To this end, we have generated an adult-inducible whole body SIRT1 knockout mouse in genetically homogeneous C57BL/6 mice based on a tamoxifen inducible CRE system. We have confirmed efficient deletion of SIRT1 in tissues including liver, heart, muscle, pancreas, cortex and kidney and observe no gross phenotypic differences between SIRT1 knockout and control mice after SIRT1 deletion. Initial findings from these experiments suggest that knocking out SIRT1 in adults does not grossly impair glucose metabolism, but these animals have dramatically impaired mitochondrial function in skeletal muscle, including decreases in mitochondrial DNA content, mitochondrial membrane potential, ATP levels, and mitochondrial gene expression. We also observe a decrease in state 3 and FCCP-induced respiration, which indicates a decrease of electron transport chain capacity, a phenotype exacerbated by a high fat diet. Preliminary examination of cardiac tissue suggests that mitochondrial function in this organ is impaired in a similar manner to that seen in skeletal muscle, while no changes were observed in mitochondria isolated from liver. Results from studies examining how SIRT1 knockout mice respond to feeding of sirtuin-activating compounds SRT1720 and resveratrol will be presented.

BIPHASIC DOSE RESPONSE IN A MODEL OF TAUOPATHY UTILIZING CYANINE DYES

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Progressive deposits of misfolded protein are a hallmark of many neurodegenerative disorders, including Alzheimer's disease. In the case of AD the tau protein, which forms amyloid type filaments, is an appealing target for intervention. Because tau plays an important role in microtubule stabilization, addressing the conformational change without inhibiting normal biology is an important issue. We have utilized a member of the cyanine dye family both in vitro, cells culture and organotypic slice cultures and in all model systems a biphasic dose response curve is observed. In cell and tissue culture models submicromolar concentrations (0.01 and 0.001 μM respectively) of the cyanine dye 3,3'-diethyl-9-methyl thiacarbocyanine iodide (C11) was capable of significantly reducing the levels of aggregated tau. However, as concentration increases inhibitory activity is lost. Finally, at concentrations above 0.3 μM tau polymerization is increased. Alterations in filament mass can also be measured at the level of individual filaments using electron microscopy with changes in filament number and total length reflecting the changes seen via immunoblotting. These effects on tau aggregation occur without changes in tau phosphorylation state. There were no changes in apoptotic or synaptic integrity markers at either does. Additionally, submicromolar concentration of C11 do not affect tau-microtubule binding, while at aggregation inducing concentrations C11 produces a decrease in microtubule bound tau. Overall, C11 modulates tau polymerization in a dose dependent manner with potential uses in therapeutics and hypothesis testing.

EARLY ENVIRONMENTAL CHANGES INFLUENCE LONG-TERM VASCULAR FUNCTION IN MICE

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The environment has a tremendous impact on cardiovascular growth, development, maturation and aging. Since the discovery that the fetal environment influences cardiovascular health in adults, much attention has been directed towards the impact of early changes in the environment on vascular function through aging. The main hypothesis of our work is that during the postnatal developmental and maturation phase, the environment permanently "shapes" the cardiovascular system. We propose that the adaptation of the cardiovascular system to a change in the environment at adulthood will be pre-determined by the maturation phase. The aim of our work is, therefore, to investigate the impact of either a sedentary lifestyle, combined or not with a treatment with catechin (an antioxidant polyphenol), or an active lifestyle of voluntary exercise, from the age of 4 weeks to 9 months; at this age, all animals are reversed to a sedentary environment alone and either under a normal or a high fat diet for another 3 months. Vascular function, structure and its molecular signature are then investigated. This study is based on our previous results showing that treatment of C57Bl/6-LDRr-/-;hApoB+/+ atherosclerotic mice with catechin starting at the age of 9 months was deleterious as evidenced by a rise in neutrophil adhesion on the native endothelium, an increase in inflammation, and a worsening of the endothelial dysfunction at 1 year. In contrast, the same treatment led to a complete reversal of the age-related endothelial dysfunction and inflammation in C57Bl/6 wild type mice, a beneficial effect that was significantly less when wild type mice were treated from the age of 3 months up to 12 months. In conclusion, our data suggest that the environment leads to a durable imprint during the maturation phase that influences the adaptation of the vascular system to a change in the environment later in life.

SIMULATION STUDIES TO COMPLEMENT OBSERVATIONAL DATA: WHAT CAN WE LEARN? HOW SHOULD THEY BE USED?

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It is common to read accounts of simulation studies accompanying research results. Occasionally, the results are in of themselves, reports on a simulation. Simulation studies can be valuable and provide insight in interpreting results of observational and experimental studies. On the other hand, simulation studies do depend on the assumptions underlying their development. We discuss use of simulation with application to secondary data analyses of assays that are based on available data- not data resulting from a controlled trial. The discussion identifies settings where simulations are of value, and also discusses limitations. Factors important in designing and reporting simulation studies are discussed in the context of an example examining low dose effects using Ames data.

POSTER SESSION

GENE EXPRESSION PROFILES OF HORMETIC EFFECTS IN *DROSOPHILA MELANOGASTER*

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Dietary restriction is a known example of hormesis - a low-dose stressor that results in a positive phenotype. We used gene-centric and pathway-centric analyses to compare gene expression data from *Drosophila melanogaster* under dietary restriction as well as genetic (Sir2 and p53 alterations) and pharmacologic (resveratrol) conditions known to extend lifespan. These studies demonstrate some of the shared responses between these different treatments and provide insights into the molecular mechanisms underlying these life span extending interventions.

ANTIDEPRESSANTS AND BREAST AND OVARIAN CANCER RISK: A REVIEW OF THE LITERATURE AND RESEARCHERS' FINANCIAL ASSOCIATIONS WITH INDUSTRY

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Background: Antidepressant (AD) use has been purported to increase the risk of breast and ovarian cancer, although both epidemiological and pre-clinical studies have reported mixed results. Previous studies in a variety of biomedical fields have found that financial ties to drug companies are associated with favorable study conclusions.

Methods and Findings: We searched English-language articles in MEDLINE, PsychINFO, the Science Citations Index and the Cochrane Central Register of Controlled Clinical Trials (through November 2010). A total of 61 articles that assessed the relationship between breast and ovarian cancer and AD use and articles that examined the effect of ADs on cell growth were included. Multi-modal screening techniques were used to investigate researchers' financial ties with industry. A random effects meta-analysis was used to pool the findings from the epidemiological literature. Thirty-three percent (20/61) of the studies reported a positive association between ADs and cancer. Sixty-seven percent (41/61) of the studies reported no association or antiproliferative effect. The pooled odds ratio for the association between AD use and breast/ovarian cancer in the epidemiologic studies was 1.11 (95% CI, 1.03-1.20). Researchers with industry affiliations were significantly less likely than researchers without those ties to conclude that ADs increase the risk of breast or ovarian cancer. (0/15 [0%] vs 20/46 [43.5%] (Fisher's Exact test P=0.0012).

Conclusions: Both the pre-clinical and clinical data are mixed in terms of showing an association between AD use and breast and ovarian cancer. The possibility that ADs may exhibit a bi-phasic effect, whereby short-term use and/or low dose antidepressants may increase the risk of breast and ovarian cancer, warrants further investigation. Industry affiliations were significantly associated with negative conclusions regarding cancer risk.

The findings have implications in light of the 2009 USPSTF guidelines for breast cancer screening and for the informed consent process.

LOW DOSE RADIATION ELEVATES ANTIOXIDANT CAPACITY IN SUBSTANTIA NIGRA AND REDUCES ROTATIONS IN 6-HYDROXYDOPAMINE-LESIONED RATS

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Oxidative damage to the nigral dopaminergic neurons has been implicated in the pathogenesis of Parkinson's disease (PD). Hence, an elevated level of antioxidants may be helpful in reducing neuronal oxidative damage and reduction of PD symptoms. We have observed marked increase in total antioxidant capacity in substantia nigra in rats subjected to 45 cGy radiation dose to the brain in comparison to controls. In order to evaluate the effect of low dose radiation on improvement of motor deficits, 6-hydroxydopamine-lesioned rats (PD model) were subjected to low dose radiation to the brain in the range of 0 to 45 cGy. Our preliminary data shows that 10 and 45 cGy radiated groups exhibited reduced number of rotations when compared to controls that were not treated with low dose radiation. The reduction in the number of rotations was greater for the rats exposed to 45 cGy when compared to those treated with 10 cGy. This could be indicative that low dose radiation exposure could reduce some symptoms of PD. If further testing confirms these observations, the progression of PD in humans may potentially be slowed using low dose radiation. There may be concerns regarding this approach in light of the belief that low dose radiation is carcinogenic based on the linear non-threshold (LNT) extrapolation of high dose data. However, there is considerable evidence against the validity of LNT extrapolation; therefore, these concerns may be invalid. In addition, since there is a large lag time for the occurrence of radiation attributed cancer from the time of irradiation, especially for low doses, control of PD through low dose radiation may lead to a net gain in the quality of life for these patients for many years, even if LNT extrapolation is believed to be valid.

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CANCER MORTALITY FOR A SINGLE RACE IN LOW VERSUS HIGH LAND ELEVATION IN THE U.S.

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It is well-known that lower land elevations have lower natural background radiation levels compared to higher land elevations. A previous ecological study analyzed cancer mortality rates for all races at the county level in the six U.S. jurisdictions (states + D.C., referred to here as "states") having the lowest average land elevations and compared their rates to rates in the six states having the highest average land elevations. The present ecological study repeats the previous study except that it analyzes rates for a single race, instead of all races, since death rates can vary by race, and since race proportions can vary by state. The race selected was the one having the largest amount of reportable data by the National Cancer Institute (race = Caucasian). Low and high elevation states were selected, as before, based on their average non-overlapping land elevations, from a U.S. Geological Survey Report. In the low land elevation group, the six states are Delaware, Washington D.C., Florida, Louisiana, Mississippi, and Rhode Island (n = 210 low elevation counties). In the high land elevation group, the six states are Colorado, Montana, New Mexico, South Dakota, Utah, and Wyoming (n = 171 high elevation counties). Average age-adjusted cancer mortality rates for 2002-2006 at the county level for this race consisted of both genders, < age 65, and all sites cancer. Cancer mortality rates for low elevation counties were compared to rates for the high elevation counties. The mean cancer mortality rate for low elevation counties was 73.47 $\pm$ 18.35 compared to 53.90 $\pm$ 13.76 for high elevation counties, a difference that was statistically significant ($p < 0.0001$) with 100% statistical power. This finding suggests the presence of radiation hormesis. Further research is indicated to verify or refute these findings.

LACK OF ASSOCIATION BETWEEN LUNG CANCER, SMOKING, AND RADON IN OREGON

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Factors thought to be related to lung cancer include smoking, radon, and educational attainment. These factors were analyzed in the present ecological study for Oregon with correlation and linear regression statistics. A moderate, inverse, and statistically significant correlation was found with educational attainment while surprisingly, negligible and statistically insignificant correlations were found with smoking and radon. More rigorous research such as case-control study designs, are indicated to verify or refute these findings.

MECHANISMS UNDERLYING GENOTOXIC THRESHOLDS IN THE LOW DOSE REGION

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Traditionally, DNA damage (genotoxicity) was assumed to be induced in a linear manner relative to dose. This paradigm was based on early "high" genotoxic dose data which was extrapolated to zero, but was assumed without detailed investigations in the low dose region. This default position has serious implications in terms of risk assessment, health management and our understanding of cancer biology.

We have challenged this position and over the past 10 years have shown that some genotoxins display instead a thresholded dose response, with low doses of some alkylating agents not inducing DNA damage (mutation and chromosome damage) in vitro (Doak et al., 2007). Recently, there has also been in vivo confirmation that low dose exposure to the alkylating agent EMS does not induce genotoxicity in a variety of mouse tissues (Gocke et al., 2009).

We have been heavily involved in investigating the mechanisms involved in low dose "genotoxic tolerance", focussing primarily on DNA repair. We have been able to show that knock-down of specific DNA repair genes removes the genotoxic tolerance to EMS in vitro and hence, that DNA repair is centrally involved in the threshold observed for this genotoxin (Zair et al., 2011). Other mechanisms investigated by ourselves include the involvement of antioxidant enzymes in genotoxicity induced by reactive oxygen species (ROS) and the role of metabolic activation (P450's) in genotoxic thresholds.

DNA repair enzymes can be up-regulated by exposure to genotoxic agents, we have demonstrated the up-regulation of MGMT and MPG after exposure to the alkyalting agents MMS and EMS, but this isn't universal as OGG1 was not up-regulated following ROS exposure. Up-regulation of repair capacity has the potential to induce hormesis in exposed tissues and indeed the in vivo studies with EMS showed a potential hormetic effect (low doses with less DNA damage than controls- Gocke et al., 2009). Our studies in vitro however have failed to show hormesis so far, with a range of genotoxins.

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EFFECT OF NICOTINE ON THE RADIATION-INDUCED BYSTANDER RESPONSE OF THE HPV-G CELL LINE

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Radiation-induced bystander effects (RIBE) even though well accepted, have poorly understood mechanisms although inter-cellular signalling is clearly important. Previous work suggested cells might be harnessing existing neurotransmitters present in trace amounts in serum to signal between irradiated and non-irradiated cells. This study is therefore aimed to investigate the effect of nicotine on production of RIBE. Nicotine, a chemical found in tobacco and tomato plants, was chosen because of its widespread use and its ability to act on nicotinic acetylcholine receptors by imitating the action of neurotransmitter acetylcholine. Additionally, recent studies have revealed that low doses of nicotine have therapeutic effects in a number of neurodegenerative diseases. Cells were irradiated with X-ray doses of 0.1, 0.5, 1, 2, 3, and 5 Gy while being exposed to different concentrations of nicotine ranging from zero to 10 mM. Cells were either left to form colonies or irradiated cell conditioned medium was harvested and transferred to recipient cells. The effects were determined using the standard clonogenic assay. The results suggest nicotine is radioprotective. It was shown that concentration of 100nM increased cell survival for all radiation doses. Results of the bystander experiment clearly showed an elevation in the number of colonies in range of 10-100 nM for different doses. This elevation was best observed in radiation dose of 1Gy. The results of the present study suggest that low concentrations of nicotine protect directly irradiated cells and also enhance RIBE in HPV-G transfected human keratinocyte cells. It is not clear what the mechanism of protection is but inhibition of apoptosis is being considered.

HUMAN LUNG CANCER RISKS FROM RADON – PART I – INFLUENCE FROM BYSTANDER EFFECTS – A MICRODOSE ANALYSIS

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Since the publication of the BEIR VI report in 1999 on health risks from radon, a significant amount of new data has been published showing various mechanisms that may affect the ultimate assessment of radon as a carcinogen, at low domestic and workplace radon levels, in particular the Bystander Effect (BE) and the Adaptive Response radio-protection (AR). We analyzed the microbeam and broadbeam alpha particle data of Miller *et al.* (1995, 1999), Zhou *et al.* (2001, 2003, 2004), Nagasawa and Little (1999, 2002), Hei *et al.* (1999), Sawant *et al.* (2001a) and found that the shape of the cellular response to alphas is relatively independent of cell species and LET of the alphas. The same alpha particle traversal dose response behavior should be true for human lung tissue exposure to radon progeny alpha particles. In the Bystander Damage Region of the alpha particle response, there is a variation of RBE from about 10 to 35. There is a transition region between the Bystander Damage Region and Direct Damage Region of between one and two microdose alpha particle traversals indicating that perhaps two alpha particle "hits" are necessary to produce the direct damage. Extrapolation of underground miners lung cancer risks to human risks at domestic and workplace levels may not be valid.

Keywords: Radon Lung cancer, Bystander, Adaptive Response, Case-control Studies

HUMAN LUNG CANCER RISKS FROM RADON – PART II – INFLUENCE FROM COMBINED ADAPTIVE RESPONSE AND BYSTANDER EFFECTS – A MICRODOSE ANALYSIS

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In the prior Part I, the potential influence of the low level alpha radiation induced bystander effect (BE) on human lung cancer risks was examined. Recent analysis of adaptive response (AR) research results with a Microdose Model has shown that single low LET radiation induced charged particles traversals through the cell nucleus activates AR. We have here conducted an analysis based on what is presently known about adaptive response and the bystander effect (BE) and what new research is needed that can assist in the further evaluation human cancer risks from radon. We find that, at the UNSCEAR (2000) worldwide average human exposures from natural background and man-made radiations, the human lung receives about a 25% adaptive response protection against the radon alpha bystander damage. At the UNSCEAR (2000) minimum range of background exposure levels, the lung receives minimal AR protection but at higher background levels, in the high UNSCEAR (2000) range, the lung receives essentially 100% protection from both the radon alpha damage and also the endogenic, spontaneously occurring, potentially carcinogenic, lung cellular damage.

HUMAN LUNG CANCER RISKS FROM RADON – PART III – EVIDENCE OF INFLUENCE OF COMBINED BYSTANDER AND ADAPTIVE RESPONSE EFFECTS ON RADON CASE-CONTROL STUDIES – A MICRODOSE ANALYSIS

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Since the publication of the BEIR VI (1999) report on health risks from radon, a significant amount of new data has been published showing various mechanisms that may affect the ultimate assessment of radon as a carcinogen, in particular the potentially deleterious Bystander Effect (BE) and the potentially beneficial Adaptive Response radio-protection (AR). The case-control radon lung cancer risk data of the pooled 13 European countries radon study (Darby et al 2005, 2006) and the 8 North American pooled study (Krewski et al 2005, 2006) have been evaluated. The large variation in the odds ratios of lung cancer from radon risk is reconciled, based on the large variation in geological and ecological conditions and variation in the degree of adaptive response radio-protection against the bystander effect induced lung damage. The analysis clearly shows Bystander Effect radon lung cancer induction and Adaptive Response reduction in lung cancer in some geographical regions. It is estimated that for radon levels up to about 400 Bq m-3 there is about a 30% probability that no human lung cancer risk from radon will be experienced and a 20% probability that the risk is below the zero-radon, endogenic spontaneous or perhaps even genetically inheritable lung cancer risk rate. The BEIR VI (1999) and EPA (2003) estimates of human lung cancer deaths from radon are most likely significantly excessive. The assumption of linearity of risk, by the Linear No-Threshold Model, with increasing radon exposure is invalid.

CASE STUDY: QUANTITATIVE ASSESSMENT OF THE BIPHASIC DOSE-RESPONSE OF POLYN-ISOPROPYLACRYLAMIDE (PNIPAM) NANOPARTICLES

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The term hormesis generally denotes a dose-response relationship that is characterized by stimulation below the toxic threshold, creating a graphical representation of a biphasic dose-response. Previous reports have shown that biphasic dose-responses are ubiquitous for a number of endpoints that have been evaluated following a response to pharmaceuticals, metals, organic chemicals, radiation, or physical stressor agents. Recent reports indicate that certain nanoparticles (NPs) may also exhibit a biphasic, or hormetic dose-response. Described here is the application of several evaluative methodologies to quantify the magnitude of the biphasic response of human keratinocyte (HaCaT) and colon cells (SW 480) exposed to polyN-isopropylacrylamide (PNIPAM) NPs over a concentration range of 25 to 1000 mg/l. This case-study is a useful example for investigators attempting to parse NP dose-response data into categories (*i.e.*, bins) based on the magnitude of hormesis.

HORMESIS: PRÉSENTATION OF A PRACTICAL APPLICATION OF HORMÉSIS LAWS IN INDIVIDUALIZED PREVENTIVE MEDICINE

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For 25 years MediPrevent, an association of French doctors, has been applying and teaching in Europe an original treatment of neuroendocrino-immunomodulation. This treatment is based on the calculation, made from biological tests, of dilutions of different biological modulators to be used in individualized prevention. Hormesis laws imply a physiological response to small doses of modulators.

This method fully distinct from homeopathy, realizes a modulation of immune and neurotransmettors networks, and of endocrine system.

Immuno-biological tests (protein profile of 19 proteins and typing of lymphocytic subsets), neurotransmettors tests and steroid tests allowed to offer immuno-modulation thanks to intestinal autonosodes prepared on the basis of bacteria found in the patient's intestinal flora, antiserums, cytokins, neurotransmettors and hormons. They are diluted according to calculation grids prepared on the basis of understanding the dynamics of physiopathological mechanisms of complex systems which evolved from deterministic chaos at random (see two Nobel Prizes works: Neils Jeme and his immune network therory, Rolf Zinkernagel (with Peter Doherty) and his works about restriction of immune reactions by HLA molecules) and of the experience stemming from the confrontation of the clinical condition with biological results. The dilutions which allow to regulate the immune system and inflammatory mechanisms range from 5th centesimal dilution (10^{-10}) up to 30^{th} (10^{-60}) or even more.

Dilutions of total immunoglobulins, total (AS) HLA DR, total AS HLA B antiserums constitute the application of hormesis principles:

-1/ The dilution has no pharmacological action (like in high doses) which is characterized by a specific action (high intensity and low ubiquity) but a NON-specific modulatory action (low intensity and high ubiquity) while acting on some elements or parameters which contributed to the appearance of physiopathological mechanisms.

-2/ The action inversion principle.

COMPUTED TOMOGRAPHY SCANS MODIFY BIOLOGICAL CONSEQUENCES OF PRIOR HIGH DOSE RADIATION EXPOSURES IN TRP53 HETEROZYGOUS MICE

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We tested if computed tomography (CT) scans could modify the consequences of a prior high dose exposure in cancer-prone Trp53 heterozygous female mice. Mice (7-8 weeks old) were exposed to a whole-body 4 Gy dose of γ-radiation (Cs-137, 0.349 Gy/min). Four weeks after the high dose exposure, mice were then given weekly single whole-body CT scans (10 mGy/scan, 75 kVp) for ten consecutive weeks [n=10]. Five days after the last CT scan, bone marrow and blood were collected and challenged *in vitro* with 0, 1, and 2 Gy (Cs-137, 0.188 Gy/min). The corresponding age-matched control groups were: i) non-irradiated controls [n=5] ii) 4 Gy-only at 7-8 weeks of age [n=5] and iii) weekly CT scans only [n=5]. The biological endpoints examined were flow cytometric micronucleated reticulocytes (MNRET), histone H2AX phosphorylation (γH2AX), DNA oxidative stress (8-OHdG), and apoptosis (Annexin V + 7AAD).

There were no differences in MNRET levels between the various mouse groups ($p>0.05$). When challenged with 1 and 2 Gy *in vitro*, all groups exhibited significant increases in γH2AX foci formation in bone marrow cell populations ($p<0.01$). Following a 2 Gy challenge, there was a 9% reduction in γH2AX foci in bone marrow lymphocytes of mice receiving only the weekly CT scans as compared to controls ($p=0.014$). Furthermore, basal levels of DNA oxidation in bone marrow lymphocytes decreased 14% in mice treated with weekly CT scans relative to the controls and 4Gy-only cohorts ($p=0.007$). DNA oxidative stress levels were also diminished by 10% after a 2 Gy challenge in CT scanned mice as compared to control mice ($p=0.038$). Similarly, mice that received weekly CT scans demonstrated 20% lower spontaneous levels of apoptosis in peripheral blood lymphocytes than mice not CT scanned ($p=0.006$). Reduced levels of apoptosis in CT scanned mice were also evident following a challenge dose of 1 Gy ($p=0.011$) and 2 Gy ($p=0.041$) relative to controls.

In conclusion, repeated CT scans can modify the biological responses of a previous high dose acute 4 Gy total body exposure in cancer-prone Trp53+/- mice. The observed reduction in both levels of DNA oxidative stress and apoptosis in mice treated with weekly CT scans supports the contention that mice can adapt to repeated low dose exposure. Overall, repeated CT scans seem to confer resistance to larger doses in Trp53+/- female mice.

THE BYSTANDER EFFECT IN HIGH DOSE RATE BRACHYTHERAPY OESOPHAGEAL CARCINOMA PATIENTS

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The bystander effect is a non-targeted phenomenon that occurs when irradiated cells emit signals which mediate damage to nearby unirradiated cells. This phenomenon needs to be studied more extensively in targeted radiotherapy which is used to *precisely* treat cancerous tissues with high doses of radiation, in a short period of time, while sparing healthy surrounding tissues. In this pilot study, the objective is to evaluate whether a radiation-induced bystander effect (RIBE) in a HPV-G cell line--a thoroughly tested reporter cell line-- can be initiated when exposed to the blood, urine and biopsy samples of oesophageal carcinoma patients undergoing high dose rate (HDR) brachytherapy. An *in vivo* clonogenic assay will be used for urine, blood sera, and media conditioned from oesophageal explants pre- and post-treatment. It is expected that the bystander effect will cause a reduction in survival of reporter cell colonies after exposure to blood sera, urine, and culture medium conditioned by esophageal biopsy post-HDR brachytherapy. Additionally, the bystander effect will be studied 3 weeks after treatment to observe whether a bystander signal remains, and this could explain some of the common side effects seen in radiation therapy patients long after their treatment is completed. As well, radiation-induced apoptosis will be assessed in both the cancerous treated tissue and whole blood samples; it is expected post-treatment that there will be an increase in apoptosis. This will indicate that HDR brachytherapy is an effective treatment, and if

such a phenomena exists wide spread in vivo, from cell to cell communication via soluble factors, then this radiation treatment which *precisely* treats cancerous tissue will be challenged. Overall, the aim is to assess whether secondary cancer can be posed as a risk to patients undergoing treatment, and the effectiveness of HDR brachytherapy will be tested by analyzing apoptosis in cancerous tissue.

ASYMMETRIC CHANGES IN THE RAT BRAIN PROTEOME FOLLOWING HIGH ENERGY X-RAY MICROBEAM IRRADIATION

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Rats were irradiated with 35 or 350 Gy MRT microbeam, applied to the right brain only, at the European Synchatron Radiation Facility, Grenoble, France. The brain was then divided into right and left hemispheres. Sections, taken from the central region of the cerebral cortex, were then analysed by 2-dimensional gel electrophoresis. Proteins which showed a change in expression in either the irradiated right hemisphere or non-irradiated left hemisphere were excised from the gels, digested and identified by mass spectrometery. In the right hemisphere increases in aconitase and triosphoshate isomerase, and a decrease in dihydrolipoyl dehydrogenase downregulation are recognised as brain tumour markers. In the left hemisphere, NADP dehydrogenase expression is increased and prohibitin is reduced. These are the opposite responses of these proteins seen in cancers. Therefore both these "bystander" responses would appear to be counter-tumourogenic. Similarly tubulin expression is known to be upregulated by UV exposure so fact that expression declined in the left hemisphere would appear to be the opposite of direct irradiation. Glial fibrillary acidic protein (GFAP) was increased in the bystander hemisphere. The relationship between changes in GFAP expression and tumourogenesis is more complex; both increased and decreased expression has been recorded during tumour development. The same applies to heat shock protein 71, the only protein found to increase in both hemispheres. Thus the significance of these proteins, with regard to pro- or anti- tumourogenesis, may depend on how their changes in expression relate to other simultaneously occurring proteomic responses.

BIOLOGICAL EFFECTS OF PET IMAGING PROCEDURES

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We investigated the biological effects of PET scans which require the administration of radiopharmaceutical F18-FDG (250 keV β+, 511 keV γ). The radiation induced response to a single PET scan was evaluated in wild type female mice using flow cytometry based endpoints: micronucleated reticulocyte formation (MN-RET) and histone H2A.X phosphorylation (γH2A.X). Mice received injections of 0, 20, 40, 100 or 400 μCi F18 FDG (n=10) corresponding to whole body doses of 0, 12, 23, 58 or 233 mGy at 7-9 weeks of age. It was first established that MN-RET levels reach a maximum at 43 hours following a PET scan (n=5). At 43 hours, a dose response was observed at doses greater than 40 μCi (23mGy) 18F-FDG ($p<0.001$). No significant increase in MN-RET levels above control levels was seen in the 0-40 μCi range ($p=0.6$). This indicates that there is a threshold for DNA damage induction in bone marrow by PET scans since the MN-RET endpoint has been shown to be sensitive to whole body doses as low as 10 mGy (n=5, $p=0.03$) with an external γ exposure (Cs-137, 0.349 Gy/m). For γH2A.X, it was observed that a 400 μCi PET scan (233 mGy) caused a significant reduction in foci levels relative to controls at 24 hours post scan ($p=0.018$). This indicates that high dose PET scans are able to cause changes in the bone marrow lymphocyte population. The biological response to PET scans was also evaluated in 47-48 week old female wild type mice. The older mice were more radiosensitive to a single scan (20, 100, 40 or 1000 μCi F18 FDG) relative to the 7-8 week old mice as measured by radiation induced MN-RET per unit dose ($p=0.012$). This shows that age plays a role in the magnitude of the radiation response experienced following a PET scan.

DETERMINATION OF ^{226}RA IN FISH USING CONVENTIONAL LIQUID SCINTILLATION ANALYSIS

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^{226}Ra is a radionuclide of much concern since it poses a high risk of radio-toxicity when ingested and is well known for its long half life of 1600 years. A simple and direct method to determine ^{226}Ra ingested by fish using a homogeneous liquid scintillation counting was developed. The fish whole body was processed by calcination and digested in aqua regia. After taking up the residue in chloride form, the resulting liquid was mixed thoroughly with the scintillator in a low potassium scintillation vial and sealed with Teflon tape before counting. The in growth of ^{222}Rn and its progeny was followed closely during counting using a β-spectrometer Liquid Scintillation Counter. ^{226}Ra activity in the fish was determined after secular equilibrium with its progeny. The minimum detectable activity was determined to be 24mBq/g for 200 minute counting. Fish which were fed with a radioactive diet of 1000mBq/g were determined to have an activity of 155mBq/g, where as the control fish activity obtained was 100mBq/g. This analysis suggests that Radium is not taken up readily in fish and may be dependent on the fish composition.

WHY HORMESIS IS THE MOST FUNDAMENTAL DOSE RESPONSE

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Hormesis, the non-linear dose response curve of toxins showing positive *stimulation* at doses below the dose where effects match the zero dose effect remains controversial and seemingly paradoxical. The usual definition of hormesis: "a process in which exposure to a low dose of a chemical agent or environmental factor that is damaging at higher doses induces an adaptive beneficial effect in the cell or organism" is problematic in that it projects a value judgment on the effects (beneficial) and implies the wrong expectation that the default dose-response curve should be monophasic.

A hypothesis is presented as to why evolution configured organisms to have hormesis as their most fundamental dose response, why we should not expect any other type of dose-response, and that we should look very carefully for artifacts in any dose response that appears to be monophasic. Our default should be the hormesis-type dose response curve for essentially all noxious stimuli.

This hypothesis provides a rationale for the physiology of hormesis, of hybrid vigor, and suggests how hormetic effects should be additive (and rarely subtractive but this subtraction is critically important) among different chemical species, suggests that the total hormetic capacity of an organism is limited, and what happens when that limit is exceeded. This is a way to determine a non-arbitrary theoretically safe exposure dose.

Recent whole genome scans on large human cohorts (thousands) of so called complex genetic disorders have found few common genes. What has been found are copy number variants, deletions or duplications of otherwise normal genes but usually with incomplete penetrance. These findings will be explained as the normal and expected hormetic physiological responses.