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HORMESIS:

IMPLICATIONS FOR TOXICOLOGY, MEDICINE AND RISK ASSESSMENT

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ABSTRACT BOOK

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MECHANISMS OF ACTION AND THERAPEUTIC POTENTIAL OF NEUROHORMETIC PHYTOCHEMICALS

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Phytochemicals present in vegetables and fruits are believed to reduce the risk of several major diseases including cardiovascular disease, cancers and neurodegenerative disorders. Although antioxidant properties have been suggested as the basis of health benefits of phytochemicals, emerging findings suggest a quite different mechanism of action. Many phytochemicals normally function as toxins that protect the plants against insects and other damaging organisms. However, at the relatively low doses consumed by humans and other mammals these same "toxic" phytochemicals activate adaptive cellular stress response pathways that can protect the cells against a variety of adverse conditions. Recent findings have elucidated hormetic mechanisms of action of phytochemicals (e.g., resveratrol, curcumin, sulforaphanes and catechins) on neurons using cell culture and animal models. Such neurohormesis pathways include those involving kinases normally activated by growth factors, the transcription factor Nrf-2 which activates genes controlled by the antioxidant response element, NF-κB, and histone deacetylases of the sirtuin family. The latter signaling proteins stimulate the production of antioxidant enzymes, protein chaperones, neurotrophic factors and other cytoprotective proteins. In several cases neurohormetic phytochemicals have been shown to suppress the disease process in animal models relevant to neurodegenerative disorders such as Alzheimer's and Parkinson's diseases and stroke. We are currently screening a panel of biopesticides in order to establish hormetic doses, neuroprotective efficacy, mechanisms of action and therapeutic potential as dietary supplements.

HOMEOSTASIS: THE YIN AND YANG OF AUTOIMMUNITY

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Much of what we know in biology and medicine comes from our study of pathological conditions. Given that natural compounds and processes are often studied in the context of diseases, many of them are best known for their unfavorable aspects. It can take many years before empirical findings, often through serendipity, lead us to realize that our negative perceptions are only part of the story. In almost all cases there is a balance, so that too much can be as bad as too little, and the optimal situation is one of homeostasis.

The perception of autoimmunity is a case in point. Autoimmunity in general, and autoimmune T cells in particular, were almost universally viewed as by-products of developmental failure, to be alleviated all together in the process of autoimmunity. Over the years researchers have sought reasons for the observed existence of autoimmunity in healthy individuals. Our group discovered that 'autoimmune' T cells recognizing specific CNS proteins (such as myelin basic protein or some of its peptides) represent the body's mechanism of defense and protection against the effects of certain physiological compounds which, under pathological conditions, are produced in harmful overabundance. Most interestingly, while attempting to reveal the underlying mechanism of such 'autoimmune' action we discovered that autoimmunity is the body's system of maintenance, at least in the CNS, and that it promotes and controls plasticity, adult neurogenesis, and cognition. If that discovery represents the yin of autoimmunity, the yang can be perceived as the phenomenon of autoimmune disease, which develops only when the autoimmune system escapes its own mechanisms of control, but in the absence of autoimmunity impairment in the CNS takes place as well. Thus, autoimmunity represents a system of homeostasis in which normal physiology is maintained unless the balance becomes disrupted by malfunction.

Relevant key references

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HOW LOW IS LOW ENOUGH? ROLE OF SCIENCE, POLICY AND PUBLIC OPINION

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During the last half of the 20th Century, statutes were passed directing federal agencies to take on the primary role of improving air, water, food, pharmaceuticals, consumer products and, in general, the environment in which people live, work and play. In a simplistic sense, the dominant theme was there are things that are bad for people and the environment and they need to be eliminated or, alternatively, reduced to levels that protect public health. Against this categorical approach that some things are good and others are bad for people, it has been recognized that some things such as vitamins and essential elements are good, even essential, for people's health at low and moderate levels of intake while they may be harmful at higher levels of intake. Two central questions that must be addressed in implementing the plethora of statutes that are intended to protect public health are (a) What should be regulated? and (b) How low is low enough to protect public health? Increasingly, some individuals, and especially scientists, have argued that science can provide the answers. Some scientists go even further – provide more funding for research and scientists will provide even "better answers." Is this premise true? A few individuals have argued that decisions on "how low is low enough?" inevitably involve policy choices that requires scientific information to be considered in a policy context. This raises questions as to who sets the policy. To what extent does public opinion influence decisions on how low is low enough? This presentation will address these issues by reviewing a series of activities the author participated in starting in the 1960s with decisions on safety of nuclear power reactors and space nuclear systems to the 2006 decision on National Ambient Air Quality Standards for Particulate Matter.

TOXICOLOGY SESSION

ACTIVATION OF ADAPTIVE CELLULAR NETWORKS AND HORMETIC DOSE RESPONSES RELATIONSHIPS

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HORMESIS WITH DRUG-INDUCED CYTOTOXICITY

Peter J. O'Brien, University College Dublin, Belfield, Dublin 4, Ireland

NON-MONOTONIC DOSE-TOXICITY EFFECTS AND BEHAVIORAL FUNCTION: LOW-DOSE IMPAIRMENTS FROM DEVELOPMENTAL PESTICIDE EXPOSURE

Edward D. Levin, Ph.D., Duke University Medical Center, Durham, NC

HORMESIS WITH HERBICIDES: GLYPHOSATE AS A CASE STUDY

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BIOLOGICAL PROPERTIES IN GENES FOR LOW-DOSE REGULATION OF THE EMBRYONIC TRANSCRIPTOME

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ACTIVATION OF ADAPTIVE CELLULAR NETWORKS AND HORMETIC DOSE RESPONSES RELATIONSHIPS

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Hormetic dose response curves occur for many endpoints associated with exposures of cells to chemical stressors *in vitro*. To date, there is less evidence for U-shaped dose response curves for toxicity endpoints that serve as the basis for establishing exposure standards in intact organisms. Lacking this direct evidence and absent any clear generalized biological mechanism for hormesis, risk assessments use threshold or low dose linear risk models. We are examining a generic biological hypothesis for hormesis: these cell-based U-shaped responses derive from common processes involved in activation of adaptive responses required to protect cells from stressful environments. These adaptive pathways extend the range of cellular homeostasis and are protective against ultimate organ system toxicity. Activation of stress responses carries a significant energetic cost to the cell, leading to decreases of a variety of basal cellular functions in stressed cells, such as proliferation and apoptosis, compared to the unstressed condition. This trade off of resources between the unstressed system and the adapted system leads to U-shaped dose response curves for precursor endpoints. We are examining this general hypothesis using a combination of cellular studies, (both in vitro and in vivo) with genomic analysis of response pathways and with computational modeling of activation of control networks by oxidative stressors, such as chlorine, and by more generic cellular stressors, such as formaldehyde. This paper outlines our progress in examining the hypothesis that activation of adaptive networks serves as a common biological mechanism for U-shaped dose response relationships and should more directly influence risk assessment. Four discrete tissue states are expected as a function of concentration and duration. These tissue states include normal function, compensatory adaptation in moderate oxidative stress, inflammation, and overt toxicity in the presence of overwhelming concentration or significant duration of stressors. These transitions can be used to refine default risk assessment practices that do not currently accommodate consideration of adaptive responses. (This abstract does not reflect Agency policy).

HORMESIS WITH DRUG-INDUCED CYTOTOXICITY

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Characteristic biphasic responses of cells to exposure to sublethal concentrations of cytotoxic drugs and chemicals. was incidentally noted for approximately half of 200 toxic drugs that were being evaluated for their effects on cell proliferation, nuclear area, and mitochondria. Studies of specific compounds such as acetaminophen, cerivastatin, diquat, fenofibrate, and zidovudine demonstrated that hormesis occurred with a wide range of parameters, including mitochondrial activity, mass, and membrane potential, with cell number, Ca-ATPase activity, and ionised intracellular calcium concentration. Various antioxidant system activities were also up-regulated prior to degenerative effects being noted, including glutathione (GSH), glucose-6-phosphate dehydrogenase (G6PD), glutathione reductase, catalase and superoxide dismutase. The early enhancement was more prominent after incubation of cells for 3 days than for 1 day. Cells have an inherent plasticity that enables them to change specific gene expression, biochemical and functional activities when exposed to adverse conditions. Positive responses to cytotoxic drugs were consistent with specific compensatory, protective adaptations that precede the progressive decompensatory reduction in cellular activities that occur as the cells are overwhelmed by the stressor. The specificity of the adapation was especially evident from drugs and chemicals whose mechanism of toxicity was well elucidated. For example the GSH-depleter acetaminophen, characteristically increased GSH and G6PD whereas production of reactive oxygen species by diquat upregulated catalase. Oxidative stress was also associated with mitochondrial proliferation. For determination of concentrations causing half-maximal inhibitory effects (IC50), the dose-response equation needed to be modified to model the hormetic response and fit the data. The low dose enhancement resulted in an apparent right-shift of the dose-response curve and increased IC50 concentration. Low-dose enhancement provided an early biomarker for detection of cytotoxic drugs at sublethal concentrations.

NON-MONOTONIC DOSE-TOXICITY EFFECTS AND BEHAVIORAL FUNCTION: LOW-DOSE IMPAIRMENTS FROM DEVELOPMENTAL PESTICIDE EXPOSURE

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Non-monotonic dose-effect functions may often be seen in toxicology because multiple mechanisms of effect seen at different chemical doses involving a variety of actions on the organism and reactions of the organism to those effects are plotted on a two dimensional graph. The complexity of actions and reactions are certainly evident with toxicant effects on behavioral function. In a series of studies with developmental organophosphate pesticide exposure, we have found that in some cases lower dose exposure causes significantly impaired choice accuracy in the radial-arm maze whereas higher dose exposure does not. This type of result supports the contention that when lowering doses, biological effect does not end when reductions in dose levels reaches zero functional effect for the first time. Any chemical has multiple mechanisms of action; some actions may contravene the effects of others. In the case of organophosphate pesticides, doses slightly above the threshold for appreciable acetylcholinesterase inhibition have been seen to have less adverse behavioral effect than lower doses, which do not appreciably inhibit acetylcholinesterase. Organophosphate pesticides like all chemicals have multiple mechanisms of action including those apart from acetylcholinesterase inhibition. The unmasking of adverse effects at low doses brings into question the safety of assuming there are no adverse biological effects in the dose range lower than that at which no effect is initially seen when lowering doses. Just as there may be beneficial hormetic function effects of chemicals at low doses below the initial no discernable effect threshold, there may be adverse effects in this low dose range as the confluence of multiple effects changes. To improve safety, this low dose range must be thoroughly characterized, particularly given this is the dose range to which the greatest number of us are exposed.

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HORMESIS WITH HERBICIDES: GLYPHOSATE AS A CASE STUDY

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In carefully conducted dose-response studies, hormesis, in terms of growth stimulation, is commonly observed with most herbicide classes and phytotoxins on at least some susceptible plant species. Perhaps the most consistent and pronounced case of hormesis with a phytotoxin is that with the synthetic herbicide glyphosate (*N*-phosphonomethyl glycine). World wide, glyphosate is the most important herbicide and its use continues to increase with the adoption of transgenic, glyphosate-resistant crops. Almost 90% of all transgenic crops grown are glyphosate resistant, and the adoption of these crops continues to increase at a rapid pace. Thus, the opportunity for effects of low doses of this herbicide on non-target plants is great. The environmental toxicology implications of this are unknown, but understanding the mechanism of the hormetic effect may clarify whether there is any significant risk. We and others have found hormetic effects of ultra low doses of glyphosate on a large number of higher plant species. The effects are generally more pronounced in species with more lignification, such as eucalyptus and coffee, but we do not know the mechanism of this hormesis. Glyphosate acts by inhibition of the shikimate pathway at the 5-enolpyruvyl-shikimate-3-phosphate synthase (EPSPS) step. This causes reductions in aromatic amino acid pools and all of the many secondary compounds arising from them, such as lignin, flavonoids, certain plant hormones, and simple phenolic acids. Although low doses of glyphosate cause hormesis in soybean, no hormesis was seen in soybeans with a transgenes encoding a glyphosate-resistant form or EPSPS. Thus, the hormetic effect appears to be due to a low level of blockage of the shikimate pathway. Results of molecular and biochemical experiments to determine the mechanism of hormetic responses to glyphosate will be reported.

BIOLOGICAL PROPERTIES IN GENES FOR LOW-DOSE REGULATION OF THE EMBRYONIC TRANSCRIPTOME

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Microarray profiling provides a surfeit of genome-wide information that can be applied to the evaluation and assessment of chemical effects. By data-mining groups of genes that respond harmoniously under well-defined experimental conditions, we can hope to gain insight into the nature of the biological responses that determine susceptibility or resistance to environmental agents. The extent to which this technology can be used to characterize the 'hormetic response' is an open question. Our research has focused on early mouse embryos; specifically, the definition of rules to link the genomic response with cellular consequences in developmental toxicity. We profiled embryonic transcripts following maternal exposure to prototype environmental agents (methylmercury, alcohol, 2-chloro-deoxyadenosine). These agents all increased the risk for fetal eye defects in a manner dependent on dose, genetic background, and therapeutic intervention (PK11195). A differentially regulated subsystem of genes was identified in the embryonic forebrain with harmonious expression in a covariance matrix under different exposure conditions. Using this signature response, we classified the embryonic transcriptome into three states with respect to disease risk: State 1 (isothermic state) being represented by normal eye development; State 2 at the biological threshold for disease (transitional state); and State 3 linked with pathogenesis of an abnormal phenotype (disease state). Preliminary evidence suggests that checkpoints for these state transitions are controlled at the level of the mitochondrion (transitional) and p53 pathway (disease). Functional annotation of genes associated with low-dose regulation of the embryonic transcriptome can provide insight into biological properties associated with the hormetic response. (Supported by grants ES09120 and AA13205 from the NIH and grant no. R82744501 from the EPA, but does not reflect agency policy)

BIOMEDICAL SESSION

MECHANISMS UNDERLYING THE BELL-SHAPED RESPONSE OF NEURONS TO GLUTAMATE
Giles Hardingham, University of Edinburgh, Edinburgh, Scotland

BIPHASIC ACTION OF STEROIDS ON NEURAL FUNCTION: MECHANISTIC AND THERAPEUTIC IMPLICATIONS
Roberta Brinton, University of Southern California, Los Angeles, CA

GENES AND SMALL MOLECULES THAT EXTEND LIFESPAN: EVIDENCE FOR XENOHORMESIS
David Sinclair, Harvard Medical School, Boston, MA

HORMESIS: DERMATOLOGIC OPPORTUNITIES AND OPTIONS
Howard Maibach, University of California, San Francisco, CA

EXPERIMENTAL AND CLINICAL INFORMATION FOR THE POSSIBLE APPLICATION OF LDR-INDUCED HORMESIS AND ADAPTIVE RESPONSE IN MEDICAL PRACTICE
Lu Cai, The University of Louisville, Louisville, KY

MECHANISMS UNDERLYING THE BELL-SHAPED RESPONSE OF NEURONS TO GLUTAMATE

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Calcium entry through the NMDA subtype of glutamate receptors has the power to determine neuronal survival or death. While too much NMDAR activity is harmful to neurons (e.g. in stroke), so is too little activity, while physiological patterns of NMDAR activity are needed to promote neuronal survival and resistance to trauma. Understanding the mechanisms behind this dichotomous signalling is an important area of molecular neuroscience with direct clinical implications: if pro-death signalling from the NMDAR could be blocked without interfering with pro-survival or plasticity signalling pathways then this may point to better tolerated and more effective anti-excitotoxic therapeutic strategies. We review published and ongoing projects in the lab that address the question of what makes an episode of NMDAR activity promote survival or death. We show that receptor location (synaptic vs. extrasynaptic) can be important in determining the nature of signals activated: extrasynaptic NMDARs are particularly good at promoting cell death, while synaptic NMDAR signalling triggers a coordinated program of pro-survival gene expression. We also present evidence that pro-death and pro-survival signalling from the NMDA receptor requires distinct subcellular pools of calcium, and that this knowledge can be exploited to selectively block pro-death signalling and reduce excitotoxic cell death in vitro and in vivo.

BIPHASIC ACTION OF STEROIDS ON NEURAL FUNCTION: MECHANISTIC AND THERAPEUTIC IMPLICATIONS

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Our scientific endeavors are a hybrid of basic science discovery and preclinical translational research. The goal of our basic science discovery is to elucidate fundamental cellular mechanisms of 1) neural defense and repair and 2) neural plasticity required for cognitive function. Our therapeutic development goal is to translate our cellular mechanistic insights into safe and efficacious therapeutics for the prevention of and rehabilitation from neurodegenerative diseases, such as Alzheimer's, Parkinson's and stroke. To achieve these goals, we have investigated the mechanisms and neurobiological outcomes of estrogens, progestins, hormone therapies and neurosteroids. Results of these analyses have yielded insights into cellular strategies required for neural defense against degenerative insults that involve multifaceted cytoplasmic and nuclear signaling cascades that converge upon the mitochondria. Further, these signaling cascades are required for gonadal hormone regulation of morphogenesis and neurogenesis. Our data indicate a healthy cell bias of estrogen action for estrogen-inducible neuroprotective and neurotrophic outcomes. In addition, dose response analyses consistently demonstrate a biphasic dose / function relationship which is characterized by ascending and descending arms of the dose response. Moreover, for certain functions, such as neural progenitor proliferation, high doses promote inhibit neural proliferation which is comparable in magnitude to the enhancement of proliferation. Lastly, different estrogens generate different dose response profiles which do not appear to be determined by their affinity for estrogen receptor alpha or beta. The healthy cell bias of estrogen action and the different dose response profiles have therapeutic implications for timing of hormone interventions and the use of single estrogen or complex estrogenic formulations for hormone therapy.

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GENES AND SMALL MOLECULES THAT EXTEND LIFESPAN: EVIDENCE FOR XENOHORMESIS

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Barring genetic manipulation, the diet known as calorie restriction (CR) is currently the most robust way to improve health and slow aging in mammals. The fact that CR works on most species, even microorganisms, implies a conserved underlying mechanism. We work under the hypothesis that CR extends lifespan because it is a mild biological stressor that activates conserved longevity enzymes such as Sir2/SIRT1. The Sir2/SIRT1 gene may have evolved in primordial eukaryotes to help them survive adverse conditions and to have been conserved to the present day in fungi, plants and animals. Interestingly, SIRT1-activating molecules (STACs) produced by stressed plants can activate Sir2/SIRT1 in yeast and animals, extending their lifespan by a mechanism akin to CR. One explanation for this cross-communication between species is the "Xenohormesis Hypothesis," the idea that stress-signaling molecules synthesized by another species in an individual's diet or immediate environment can activate longevity pathways within that individual, thus giving the individual advance warning of a deteriorating environment and/or food supply and providing the health benefits of CR. The latest data using STACs to improve health and extend lifespan of mammals will be presented.

Hormesis: Dermatologic Opportunities and Options

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Skin, readily reachable in most species– including man– provides an open port to mammalian physiology, pharmacology and toxicology, for skin itself as well as access to the function of other organ systems (blood, etc.). Technological advances such as the vast new arena of skin bioengineering broadens the opportunities and options. What is lacking– data and interest– should be readily obtainable and evocable.

EXPERIMENTAL AND CLINICAL INFORMATION FOR THE POSSIBLE APPLICATION OF LDR-INDUCED HORMESIS AND ADAPTIVE RESPONSE IN MEDICAL PRACTICE

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Distinct effects of low-dose radiation (LDR) from those of high-dose radiation has been recognized more than 20 years ago, and extensively confirmed by subsequent studies in cultured cells *in vitro* and tissues *in vivo,* as shown by a stimulating effect on cellular metabolism, antioxidant activities and cell proliferation, known as hormesis, and also a resistance to subsequently radiation- or chemical-induced damage, called adaptive response. However, due to the public fear of radiation and the current so-called linear no-threshold model that has been and is used as the base for national and international radiobiological protection organizations, few studies on the potential application of these LDR-induced hormesis and adaptive response in clinical setting have been explored.

Several studies have shown the induction of stimulatory effects of LDR on hematological and immunological functions and also enhancing tissue antioxidant action. The stimulating effects on bone marrow cells results in a peripheral mobilization of stem cells which is greatly useful for us to develop the tissue regenerating approach to rescue organ's dysfunction. The stimulating effects on immunological function result in a significant suppression of spontaneous tumors and tumor metastasis. The enhancing tissue antioxidant action leads to a resistance of normal tissue to radio- or chemo-therapy-induced side-toxic effects. All these exciting phenomenon are urgent to be explored to define whether low-dose radiation can be used in clinics, however, there remains concern whether low-dose radiation can also stimulate tumor cells which may accelerate the development of tumors and also stimulate tumor cell metastasis. Our current study systemically proved that LDR could induce such stimulating effect on cell proliferation and also a resistance to subsequent radio-therapeutic effect in normal cells, but not in tumor cells in vitro and in vivo. Therefore, we would like to summarize the current status on this topic in this presentation.

MULTIPLE STRESSORS AND HORMESIS SESSION

WHICH DNA DAMAGE IS LIKELY TO BE RELEVANT IN HORMETIC RESPONSES?

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Jamie R. Milligan, University of California at San Diego, La Jolla, CA
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INTERACTIONS BETWEEN CHEMICALS AND RADIATION - 2+2 MAY NOT EQUAL 4

John D. Zimbrick, Colorado State University, Fort Collins, CO
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Oleksandr Moskalenko, Colorado State University, Fort Collins, CO

BIOLOGICAL MECHANISMS OF RADIATION/CHEMICAL INTERACTIONS WHICH COULD LEAD TO HORMETIC RADIOPROTECTIVE EFFECTS

Carmel Mothersill, McMaster University, Hamilton, Ontario, Canada

HORMESIS IN JOINT ACTION STUDIES WITH PHYTOTOXINS FROM *PARTHENIUM HYSTEROPHORUS* L.

Regina G. Belz, University of Hohenheim, Stuttgart, Germany

TARGETED RADIOTHERAPY: MICROGRAY DOSES AND THE BYSTANDER EFFECT

Robert J. Mairs, Glasgow University, UK Beatson Laboratories, Glasgow, Scotland
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HORMETIC EFFECTS AND LEGAL DIFFICULTIES

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WHICH DNA DAMAGE IS LIKELY TO BE RELEVANT IN HORMETIC RESPONSES?

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Working under the assumption that hormesis is triggered by specific types of DNA damage, we will focus on the types of damage which form the signature of ionizing radiation. The signature damage is comprised of complex damage, that is damage arising from clusters on ionizations such that more than one site within a 10 base pair segment of DNA has been chemically altered. In this talk, we will provide an overview of what is currently known about the formation of complex damage. Drawing primarily on recent studies that utilize electron spin resonance and product analysis to measure direct damage in plasmid DNA, yields of specific types of complex damage and a working model describing the formation of the primary damage products will be presented.

INTERACTIONS BETWEEN CHEMICALS AND RADIATION - 2+2 MAY NOT EQUAL 4

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Relatively few mechanistic studies have been carried out on the interaction of radiation and chemicals in tissues or whole organisms. Part of the reason for this lies in the complexity of cellular processes which may be affected in various ways when combinations of ionizing radiation and chemicals perturb these processes. How can we approach the design of mechanistic studies on combined exposures in model systems such that the results can be used to help elucidate molecular mechanisms underlying the observed responses, which could be additive, synergistic or antagonistic? One approach is to select a chemical agent that acts in ways similar to those found with ionizing radiation. We will use the example of Cadmium (Cd), a soluble metal ion found in numerous waste sites around the United States, and gamma radiation from Cesium-137, a radioactive isotope found in a number of the same waste sites. Cd acts via a number of mechanisms. For example it can activate oncogenes, induce apoptotic cell death, enhance cellular proliferation, inhibit DNA repair, and induce reactive oxygen free radical species. Gamma radiation also acts via these mechanisms. We are studying the combined actions of Cd and gamma radiation in an established model organism for genotoxicity and carcinogenicity testing, the Japanese medaka fish [Oryzias latipes], as well as in cultured medaka fibroblast cells. We examine endpoints that include markers of DNA damage (8-OHguanine and double-strand breaks) and we study the response of several genes known to be involved in DNA repair. Our results show that combined exposures can produce effects on our endpoints, which are greater than additive compared with the effects of each agent separately. We will discuss possible mechanisms by which these results can be explained.

BIOLOGICAL MECHANISMS OF RADIATION/CHEMICAL INTERACTIONS WHICH COULD LEAD TO HORMETIC RADIOPROTECTIVE EFFECTS

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If the question of multiple agents interacting in biological systems is considered at all, it is generally assumed that the effects will be additive. However there are both chemical and biological reasons why interactions are likely to be non-linear leading to hormetic effects of low combined doses of chemicals with radiation. Chemical reasons are being considered in another paper. Among the biological reasons are:

1. The induction of adaptive or protective responses by chronic exposure to one agent, making the organism or cells more able to withstand a second challenge,
2. Saturation of receptors for agents such as bystander signals so that exposure to another agent cannot increase the effect.
3. Interference between agents at the mechanistic level such as could occur if a pro-apoptotic agent was present during exposure to an anti-apoptotic agent.
4. Threshold effects – for example in the transition from low dose hypersensitivity to induced radioresistance, a modulating protective or sensitizing chemical could push the threshold for the transition.

This presentation will consider examples of the above situations taken from the author's own laboratory and from the published literature. The emphasis will be on identifying mechanisms leading to hormetic effects and considering how these mechanisms could be exploited in radiation protection, bio-terrorism and therapeutic prevention of normal tissue damage.

HORMESIS IN JOINT ACTION STUDIES WITH PHYTOTOXINS FROM *PARTHENIUM HYSTEROPHORUS* L.

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The invasive weed *Parthenium hysterophorus* L. biosynthesizes and releases several phytotoxins that are believed to play a role in the plant's interference with surrounding neighbours. Among these phytotoxins are sesquiterpene lactones (parthenin and tetraneurin-A) and phenolic acids (caffeic, ferulic, and vanillic acid). Both sesquiterpene lactones showed marked hormesis (y_{max} > 160 % of control) in single compound dose-response bioassays, while phenolics did not. Parthenin is believed to be the most important phytotoxin, however, as tetraneurin-A and phenolics are produced simultaneously, it is likely that binary or ternary mixtures of these compounds determine the interference potential of *P. hysterophorus.* In order to understand the joint action of these phytotoxins and its implications for hormesis effects as well as the plant's interference potential, the joint action of binary mixtures was studied using the additive dose model (ADM). The bioactivity of fixed-ratio mixtures on root growth of *Lactuca sativa* L. was evaluated in bioassays and response values were estimated by nonlinear regression analysis. Binary mixtures of both hormetic sesquiterpene lactones responded synergistically regarding the inhibition of root growth at higher doses, while the maximum stimulation of root growth (y_{max}) at low doses showed no mixture effects and followed the ADM. Binary mixtures of parthenin and phenolics showed antagonistic responses at higher doses, while the hormetic effect showed again no significant mixture effects and did not deviate from additivity. Accordingly, the hormetic effect declined with increasing ratio of phenolics as they did not exhibit hormesis. These results reveal that joint action responses are relevant for natural mixtures of phytotoxins from *P. hysterophorus*, however, only at inhibitory doses while hormesis effects seem unaffected. This suggests that hormesis may be relevant for the plant's interference, yet, the ratio of phytotoxins simultaneously released from plant material will determine if a hormetic interference will occur.

TARGETED RADIOTHERAPY: MICROGRAY DOSES AND THE BYSTANDER EFFECT

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Indirect effects may contribute to the efficacy of radiotherapy by sterilizing malignant cells that are not directly irradiated. However, little is known of the influence of indirect effects in targeted radionuclide treatment. We compared γ-radiation-induced bystander effects with those resulting from exposure to three radiohaloanalogues of meta-iodobenzylguanidine (MIBG): [^{131}I]MIBG (low linear energy transfer (LET) β-emitter), [^{123}I]MIBG (high LET Auger electron emitter), and meta-[^{211}At]astatobenzylguanidine ([^{211}At]MABG) (high LET α-emitter). Cells exposed to media from γ–irradiated cells exhibited a dose-dependent reduction in survival fraction at low dosage and a plateau in cell kill at > 2 Gy. Cells treated with media from [^{131}I]MIBG demonstrated a dose–response relationship with respect to clonogenic cell death and no annihilation of this effect at high radiopharmaceutical dosage. In contrast, cells receiving media from cultures treated with [^{211}At]MABG or [^{123}I]MIBG exhibited dose-dependent toxicity at low dose but elimination of cytotoxicity with increasing radiation dose (i.e. U-shaped survival curves). Therefore radionuclides emitting high LET radiation may elicit toxic or protective effects on neighboring untargeted cells at low and high dose respectively.
We conclude that radiopharmaceutical-induced bystander effects may depend on LET and be distinct from those elicited by conventional radiotherapy.

HORMETIC EFFECTS AND LEGAL DIFFICULTIES

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The hormetic response is a complex systems response that involves not only the responding cell but also surrounding (and not immediately affected) cells. We have demonstrated this in our laboratory through a positive bystander effect. However, the same cell type can also show a negative bystander effect; the response then is dictated by the surrounding cells (the system). This introduces an element of unpredictability into the response, as the response is determined by the status of the surrounding cells and not necessarily the type of insult.

This non-linear response makes legislation difficult as the response is determined (at least at low doses) by the state of the surrounding cells and not the damage to the targeted cell. The same dose could therefore be beneficial or lethal depending on the system biology. The other legal issue to be addressed is that of causation – was the response caused by the insult or the system? The difficulties that hormesis poses for regulators will be discussed.

RADIATION SESSION

MECHANISMS UNDERLYING THE EXPRESSION OF LOW DOSE GAMMA-RAY-INDUCED ADAPTIVE RESPONSES IN HUMAN AND RODENT FIBROBLASTS

Edouard Azzam, New Jersey Medical School, Newark, NJ

EVIDENCE FOR RADIATION HORMESIS IN HUMAN LYMPHOCYTES

Kanokporn Noy Rithidech, Stony Brook University, Stony Brook, NY
Bobby R. Scott, Lovelace Respiratory Research Institute, Albuquerque, NM

CONFERRAL OF IMMUNITY TO CANCER AND OTHER DISEASES BY CONTINUOUS LOW DOSE RADIATION

Brenda Laster, Ben Gurion University, Beer Sheva, Israel
Ilana Nathan, Ben Gurion University, Beer Sheva, Israel
Jacob Gopas, Ben Gurion University, Beer Sheva, Israel
John Kalef-Ezra, University of Ioannina Medical School, Ioannina, Greece

LOW DOSES, CROSS ADAPTATION AND MULTIPLE STRESSORS

Ron Mitchel, Atomic Energy of Canada Limited, Chalk River, ON, Canada
Marilyne Audette-Stuart, Atomic Energy of Canada Limited, Chalk River, ON, Canada
Tamara Yankovich, Atomic Energy of Canada Limited, Chalk River, ON, Canada

EXPLORING THE MECHANISMS OF THE RADIOADAPTIVE RESPONSE AT CHERNOBYL

Brenda Rodgers, Texas Tech University, Lubbock, TX
Jeffery K. Wickliffe, University of Texas Medical Branch, Galveston, TX
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Ronald K. Chesser, Texas Tech University, Lubbock, TX

RECENT BIOLOGICAL RESULTS AGAINST THE VALIDITY OF THE LNT HYPOTHESIS

Dietrich Averbeck, Institut Curie-Section de Recherche, Orsay Cedex, France
Didier Boucher, Institut Curie-Section de Recherche, Orsay Cedex, France

IT'S TIME FOR A NEW LOW-DOSE RADIATION RISK ASSESSMENT PARADIGM—ONE THAT ACKNOWLEDGES HORMESIS

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MECHANISMS UNDERLYING THE EXPRESSION OF LOW DOSE γ-RAY-INDUCED ADAPTIVE RESPONSES IN HUMAN AND RODENT FIBROBLASTS

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Health risks to humans exposed to low dose ionizing radiation remain ambiguous, and are the subject of intense debate. The need to establish risk assessment standards based on mechanisms underlying low-level radiation effects has been recognized as critical to adequately protect people and to make the most effective use of national resources. To investigate low dose/low dose-rate effects, we used γ-irradiated normal human fibroblasts adapted to grow in three-dimensional architecture that mimics cell growth *in vivo*. We determined cellular, molecular and biochemical changes in these cells. Exposure to doses ≤0.1 Gy over 48 h reduced the frequency of chromosomal damage to levels lower than background. The latter treatments also up-regulated cellular content of the antioxidant glutathione, and protected against chromosomal damage induced by a subsequent challenge dose of γ-rays. The induced mitigating effects were transient and disappeared by 48 h. DNA repair, cell cycle checkpoints, and oxidative metabolism are involved in the induced responses.

Studies of mitochondrial protein import and membrane potential also showed that effects at low dose cannot be predicted from effects at high dose radiation. They argue that induced signaling events act to alter linearity of the dose-response.

The observations with human cells mirrored effects in mouse embryo fibroblasts. Contrary to the predictions of the linear-no-threshold (LNT) model, which foresees that any dose of radiation, no matter how small, increases cancer risk, chronic exposure to γ-ray doses from 0.001 to 0.1 Gy reduced the frequency of neoplastic transformation to levels below the spontaneous rate. Furthermore, exposure to these low doses protected against chromosomal damage and neoplastic transformation from a subsequent irradiation challenge.

Long-term effects on mitochondrial physiology, checkpoint regulation and senescence in progeny of irradiated cells will be presented. We suggest that biological responses together with biophysical considerations predict the outcome of cellular exposure to ionizing radiation.

EVIDENCE FOR RADIATION HORMESIS IN HUMAN LYMPHOCYTES

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Our previous research has demonstrated that low doses of low-LET photon (X or gamma rays) or particulate radiation (protons) can induce protective effects that lead to hormetic dose-response curves for stochastic-radiobiological effects such as neoplastic transformation. For electromagnetic radiation sources, the dose range for suppressing the biological response below the spontaneous level depended on photon energy. Using micronucleus occurrence *in vitro* among irradiated human lymphocytes as a biological marker for genomic damage to cells, we have further investigated the influence of photon energy on radiation hormesis. Experiments were carried out using three different photon sources (662-keV gamma rays, 70-kVp X-rays, and 250-kVp X-rays). The micronucleus hazard h_1 [where $h_1=-ln(1-p_1)$] was evaluated in each case, and used to develop dose-response relationships. Here p_1 represents the proportion of surviving lymphocytes with one or more micronuclei. A hormetic dose-response curve was obtained for h_1 vs. dose for gamma rays but not 70-or 250-kVp X-rays. When only high-level damage [$h_2 = -ln(1-p_2)$, where p_2 is the proportion of surviving cells with 2 or more micronuclei] was evaluated, hormetic dose-response curves were revealed for 662-keV gamma rays and 70-kVp X-rays but not for 250-kVp X-rays. These results indicate that radiation hormesis occurrence depends strongly on photon radiation energy and on the nature of the biological damage assessed. Weak hormetic responses were revealed for micronucleus induction (h_1 and h_2) in human lymphocytes irradiated *in vitro* by 1.5-MeV or 13.7-MeV but not for 0.22-, 0.44-, or 5.9-MeV neutrons. The occurrence or absence of neutron-induced hormesis may relate to characteristics of the induced gamma rays and recoil protons. Our results indicate that the occurrence or absence of radiation hormesis depends on photon and neutron energy and on the nature of the biological damage considered. We conclude that low doses of neutrons and ionizing photon radiation may in some cases lead to a reduction in risk of stochastic radiobiological effects rather than an increase.

CONFERRAL OF IMMUNITY TO CANCER AND OTHER DISEASES BY CONTINUOUS LOW DOSE RADIATION

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We postulate a model in which a continuous low dose of ionizing radiation to the whole-body produces an amount of hydrogen peroxide (H_2O_2) capable of inducing an adaptive immune response. Radiation is known to produce reactive oxygen species (ROS), and their derivative, H_2O_2, during the radiolysis of water. Thus, radiation interaction with body water, the major component of living tissue, can produce H_2O_2 in quantities that would be largely dependent upon the total radiation dose, dose rate, and area of exposure. It is also known that the responses of cells and tissues to various endogenously-administered concentrations of H_2O_2 range from beneficial to harmful. H_2O_2, in low concentrations, has been shown to mimic the action of a ligand, and induce phosphorylation of the same proteins that are phosphorylated upon antigen stimulation, acting as a second messenger in lymphocyte activation[1]. These phosphorylated proteins are recognized by Toll-like receptors present on epidermal dendritic cells (the first to experience any changes in the H_2O_2 concentration). The receptor initiates a signaling pathway that causes the migration of the dendritic cells to the lymph nodes and results in an innate immune response that further instructs for the more specific adaptive immune response. Because the model envisions a system that is strongly H_2O_2 concentration-dependent, the critical constraints for the conferral of immunity are the total radiation dose to the whole body, and the rate at which it is delivered. We contend that the delivery of continuous low dose rate radiation to the entire body will induce memory in T and B cells and confer immunity to subsequent higher doses. Significantly, because the innate response is less specific than the adaptive, the initial stimulation by continuous low dose radiation might confer a generalized immunity to the early stages of cancer and other diseases. We acknowledge the Jerry Cohen Foundation, and particularly Jerry Cohen, for his assistance in advancing this hypothesis.

"Sometimes scientific progress is not based on a discovery or the generation of new data but on a change of viewpoint that allows one to see a set of already existing data in a new light." Reth

[1]Michael Reth. Hydrogen peroxide as second messenger in lymphocyte activation. Nature Immunology (2002) 3:1129 – 1134

LOW DOSES, CROSS ADAPTION AND MULTIPLE STRESSORS

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Exposure to mild thermal, chemical or radiological stress has been shown to induce an adaptive response in virtually every type of cell and organism that has been examined. This adaptive response protects the cells and organisms from the effects of a more severe stress.

However, environmental stress outside of the laboratory commonly involves multiple stressors, either simultaneously or sequentially. We have examined the ability of organisms to adapt and develop resistance to one stressor after low dose exposure to the same or different stressors. We have now also examined adaptation after low dose exposure to two or three different stressors. We have observed a general ability for an exposure to one stressor to initiate an adaptive response against the same or different stressor. However, an exposure to two or more different adapting stresses may result in excess stress, such that no adaptive response occurs and the cells are not protected against a subsequent higher stress.

These data show that the adaptive response is a general response to stress, and that cross adaption to a variety of stressors will occur. However, because it is a general response to stress, low dose exposure to multiple stressors may result in a cumulative effect that is outside the range at which the cells can initiate an adaptive response.

EXPLORING THE MECHANISMS OF THE RADIOADAPTIVE RESPONSE AT CHERNOBYL

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The genetic consequences resulting from environmental exposure to ionizing radiation have a significant impact on both radiation regulatory policies and the comprehension of the human health risks associated with radiation exposure. The Chernobyl environment is composed of low-LET, low dose-rate ionizing radiation (IR), primarily γ radiation from ^{137}Cs and ^{90}Sr and is unique as a natural laboratory in which environmental exposures to IR can be assessed. Previous studies conducted by our research team in Chernobyl, utilizing a variety of endpoints, have demonstrated no increase in mutagenesis in either native species or inbred strains of laboratory mice experimentally exposed to the Chernobyl environment. Rather than deleterious effects from exposure, a radioadaptive, or protective response has been documented in all cases. The lack of detectable mutations is likely the result of physiological alterations that mitigate the deleterious effects of ionizing radiation. To gain insight into the mechanism of the radioadaptive response, additional experiments were conducted examining transcriptional responses in genes thought to play a role in radioadaptation. Transcriptomics (quantification of mRNA levels) using oligonucleotide genearrays encompassing virtually the entire mouse genome was employed to provide the broadest possible view of potential responses. Genes expected to respond to insult from IR with altered transcription levels include those crucial to oxidative stress, DNA repair, cell cycle regulation, oxygen radical scavenging and apoptosis pathways. Ingenuity Pathway Analysis ® ver 4.0 was employed to assess relationships between genomic networks and to determine involvement in the cellular processes in question. Only a single DNA repair gene was differentially expressed in irradiated animals versus controls. No genes known to directly interact with primary DNA repair proteins exhibited altered levels of transcription. Altered transcription levels were observed in a significant portion of the machinery of the apoptosis pathway.

RECENT BIOLOGICAL RESULTS AGAINST THE VALIDITY OF THE LNT HYPOTHESIS

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The linear non-threshold (LNT) hypothesis implies that cells, tissues and organisms respond to ionizing radiation (IR) by expression of radiation damage linearly with dose. Similarly, IR-induced long term risks from the induction of mutation and cancer are thought to be linearly linked to radiation dose favouring extrapolations from high to low dose effects. Recently, this concept has been challenged by new radiobiological data based on molecular analysis of cellular and tissue responses. For statistical reasons, epidemiological studies were found not sensitive enough to deal wth human risk estimations at very low exposure levels. An important breakthrough came from fundamental studies on the mechanisms of low dose and low dose-rate effects of IR at the level of cells, tissues and organism. Cells possess a remarquable capacity to react to internal and external stresses. Molecular analyses brought to light potent defence systems which assure the maintenance of genetic stability and cellular functions especially at low IR exposure levels. At very low doses (1 mGy) IR-damaged cells are apparently eliminated from the cell population, whereas at slightly higher doses (5 mGy) DNA repair is activated, and at higher doses DNA repair or apoptosis occur. Furthermore, at low doses and dose rates the activation of antioxidant defenses, induction of genes and DNA damage signalling clearly differs from that observed at high doses and dose rates. As indicaed by the report of the French Academies these findings directly concern cell survival, mutagenesis and radiocarcinogenesis and contradict the overall validity of the LNT hypothesis. In addition, phenomena such as low dose hypersensitivity, genomic instability, adaptive response, bystander effects specifically modulate responses to low IR –exposure.

IT'S TIME FOR A NEW LOW-DOSE RADIATION RISK ASSESSMENT PARADIGM–ONE THAT ACKNOWLEDGES HORMESIS

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The current low-dose radiation risk assessment paradigm for humans is based on the premise that exposure to any amount of ionizing radiation (e.g., neutron, alpha, beta, or gamma forms or their combination) is harmful and the risk of cancer occurrence increases as a linear no-threshold (LNT) function of dose. The current system of radiation protection for humans is based on the LNT risk-assessment paradigm. Perceived harm to the irradiated workers and public is mainly reflected through calculated hypothetical increased cancers. The LNT-based system of protection employs easy-to-implement measures of radiation exposure. Such measures include the equivalent dose (a biological-damage-potential-weighted measure) and the effective dose (equivalent dose multiplied by an organ-specific relative sensitivity factor for stochastic effects). These weighted doses have special units such as the sievert (Sv) and millisievert (mSv, one thousandth of a Sv). Radiation-induced harm is controlled via enforcing exposure limits expressed as effective dose. Effective dose is also widely used for calculating expected cancer cases for a group or population exposed to low-level radiation (e.g., persons exposed to low-level radiation from the Chernobyl accident; persons exposed in their homes to radon). For every such effective dose, one can assign a hypothetical risk for cancer occurrence, using established LNT-based risk coefficients. Expected cancer cases can be easily computed based on the summed effective dose (person-Sv) for an irradiated group or population. Yet the current system of radiation protection needs revision because radiation-induced natural protection (hormesis) has been neglected. A novel, nonlinear, hormetic relative risk model for radiation-induced cancers is discussed in the context of establishing new radiation exposure limits for nuclear workers and the public. Research supported by the Office of Science (BER), U.S. Department of Energy Grant DE-FG02-03ER63657.