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BIOMEDICAL IMPLICATIONS OF HORMESIS

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An overview of the potential biomedical implications of hormesis will be presented. It includes an assessment of the occurrence of hormetic dose responses with respect chemotherapeutics across a broad spectrum of clinical conditions (e.g., tumor-cell type responses, antibiotics, anti-viral, cognitive dysfunction), anti/pro-angiogenesis, cardiovascular/renal, neural dermal and other systems, regulatory peptides, immuno-modulatory agents, and related substances. Emphasis will be placed on an assessment of the quantitative features of their dose-response relationships and how this knowledge may be exploited in both research and clinical strategies. Underlying mechanistic foundations of the hormetic biphasic dose response relationships will be explored and assessed for their likely biomedical implications.

BIOLOGICAL SWITCHING MECHANISMS AND DOSE RESPONSE RELATIONSHIPS

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Biological signaling modules – such as nuclear transcriptional receptors, kinase/phosphatase cascades, G-coupled protein receptors, etc. – are regulated by specific proteins and small molecule ligands. These signaling modules have composite dose response behaviors in relation to concentrations of their protein components and of endogenous signaling molecules. These signaling modules comprise "molecular circuits". The behavior of the circuitry arises from the biological components and the interactions within these signal transduction pathways. Many of these molecular circuits have non-linear dose response behaviors for endogenous ligands and for exogenous toxicants. These circuits include switches with "all-or-none" responses over a narrow range of concentration. In turn, these biological switches regulate large-scale cellular processes, e.g., commitment to cell division, cell differentiation, and phenotypic alterations. Inappropriate activation or repression of these switches by exogenous compounds may lead to toxic responses. Computational simulation models of some of these pathways, such as those for MAPK kinase and for cell cycle regulation, illustrate bistable states and switching phenomena. Biologically based dose response (BBDR) models for xenobiotics that account for biological switches promise to improve risk assessment by accounting for non-linear processes in toxicology. Such BBDR/simulation models need to account for normal control of these motifs by endogenous signaling molecules and for perturbations by toxic compounds. This paper describes several of these biological switches, current tools available for constructing computational biology models of these processes, and the potential value of these models in human health risk assessment.

THE BYSTANDER EFFECT: RECENT DEVELOPMENTS AND IMPLICATIONS FOR UNDERSTANDING THE DOSE-RESPONSE

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The bystander effect refers to the biological response of a cell resulting from an event in another adjacent or nearby cell. Such effects depend upon intercellular communication, and amplify the consequences of the original event. These responses are of particular interest in the assessment of ionizing radiation risk since at public or occupational exposure levels not every cell receives a radiation track. Current radiation protection regulations and practices are based on the assumption of a linear increase in risk with dose, including low doses where not all cells are hit. Mechanisms that amplify biological effects are inconsistent with these assumptions. Evidence suggests that there are two different bystander effects in mammalian cells. In one type, a radiation track in one cell leads to damaging, mutagenic and sometimes lethal events in adjacent, unhit cells. In the other type, a radiation track in one cell leads to an adaptive response in bystander cells, increasing resistance to spontaneous or radiation-induced events. This paper describes some of the data for radiation induced bystander effects *in vitro* and correlates that data with *in vitro* and *in vivo* observations of risk at low doses. The data suggest that beneficial bystander effects outweigh detrimental effects at doses below about 100 mGy, but that the reverse is true above this threshold.

THE POTENTIAL IMPACT OF HORMESIS ON RISK ASSESSMENT

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The concept of chemical hormesis, as defined by low-dose stimulation followed by higher-dose inhibition, has a long history as a scientific hypothesis, but virtually no application in the disciplines of regulatory toxicology and human health risk assessment. The phenomenon of a toxic agent that is detrimental to human health above a certain threshold level, but which may induce positive effects at a dose that is significantly lower than the NOAEL, is not accommodated by the current risk assessment paradigm. For example, hormesis contradicts the commonly used linear dose-response models for assessing carcinogenic dose-response, and a different model would be needed to describe it. However, the existence of hormesis actually impacts all components of quantitative risk assessment in a substantive and profound manner. The importance of modifying the existing risk assessment framework to address hormesis is illustrated through a case-studies approach, which focuses on risk assessments of dioxin and PCBs as examples.

THE IMPLICATIONS OF NON-LINEAR EFFECTS IN RISK ASSESSMENT HARMONIZATION

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The fundamental question that drives risk assessment theory and policy is "What is the impact of low doses of chemicals on people?" This question represents a perpetual state of uncertainty for risk assessors/managers, because evidence of human health effects from low-level chemical exposures is rarely/never empirically determined. Instead, risk estimates are most often extrapolated from laboratory animal (primarily rodent) studies with high-dose exposures. Occasionally, risk estimates are derived from complex statistical models attempting to predict subtle, biologically based changes in people. But, in either case, the risk assessor is left with the dilemma of choosing "linearity" (the common default inference for cancer) or non-linearity (the common default (threshold) inference for non-cancer health effects). The presence or absence of non-linear effects can have considerable implications for regulatory risk assessment and management. "Harmonization" attempts to reconcile these contradictory assumptions under one paradigm. Proponents of a probabilistic and linear approach to harmonization cite variability in human susceptibility as an argument against nonlinearity (i.e. extensive variability suggests that some individuals may be exquisitely sensitive at exposures well below threshold levels for others). We will discuss the implications of this argument and compare it to what is known regarding human biological variability in general. We will also discuss the regulatory implications of hormesis within this framework.

ECONOMIC IMPLICATIONS OF HORMESIS

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Implications for economic decision making about human exposure to agents that are beneficial at low exposure but harmful at high exposure will be examined. Specific topics include estimating risk at low exposure, optimization of exposure as contrasted with setting bounds within which economic agents may choose, and implications for economic-incentive regulatory mechanisms, such as taxes and tradable permits.

An economic decision-making perspective considers the probability and magnitudes of potential benefits and harms, combining these into an "expected net benefit." When there is uncertainty about whether the exposure-response function for a particular agent exhibits beneficial effects at low dose, the expected risk depends on the magnitude of the beneficial effect and its probability, as well as the magnitude and probability of adverse effects. In the case where the beneficial effect, if it exists, is small, the expected risk may be of the same order of magnitude as the risk associated with a linear no-threshold model, multiplied by the probability that the linear model is valid.

SESSION II: RADIATION

ASSESSMENT OF LOW-DOSE RADIATION RISK IN EUROPE: DIVERGING AUTHORITIES AND SCIENTISTS

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RESPONSES TO LOW DOSES OF IONIZING RADIATION IN BIOLOGICAL SYSTEMS

Ludwig E. Feinendegen, Heinrich-Heine-University Düsseldorf, Germany
Myron Pollycove, University of California San Francisco Medical School, San Francisco, CA

RADIATION-INDUCED CHANGE IN CELL PROLIFERATION AND ITS NEUROENDOCRINE REGULATION: DOSE-RESPONSE RELATIONSHIP AND PATHOPHYSIOLOGICAL IMPLICATIONS

Shu-Zheng Liu, MH Radiobiology Research Unit, Jilin University Health Sciences Center Changchun, China

LOW-DOSE RADIATION AND GENOTOXIC CHEMICALS PROTECT AGAINST STOCHASTIC BIOLOGICAL EFFECTS

Bobby R. Scott, Lovelace Respiratory Research Institute, Albuquerque, NM
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LOW DOSE RADIATION HEALTH AND MEDICAL BENEFITS: A CENTURY OF HARD DATA AND SOFT SCIENCE

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ASSESSMENT OF LOW-DOSE RADIATION RISK IN EUROPE: DIVERGING AUTHORITIES AND SCIENTISTS

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The discrepancy between large fluctuation of natural exposures, exceeding 1-10 mSv/y without detrimental health effects, and the restrictive (1 mSv/y) limits for "artificial" population exposures become increasingly problematic for the credibility of radiation protection regulations. E.g. in Germany, the release limits correspond to 0.01 mSv/y, and requirements for the storage of waste are one million y. The cost/benefit assessment of such measures becomes particularly serious when socio-economic consequences are not restricted any more to less developed economies, but also interfere with social structures in formerly more affluent countries. Radiation protection should not become a luxury which only a few rich nations can afford.

The so far dominating over-cautious formalistic regulators prefer, to a large extent under political pressure, the "official" LNT hypothesis of IAEA. Thus assuming, for example, for residential radon a lung cancer increase of about 10 % per 100 Bq/m³, results – according to the current EU regulations – to frightening numbers, even if extensive P.R. efforts to convince the public of such dangers largely failed. Currently ICRP is extending its dose limit-setting beyond human individuals and populations to limits for animals and plants, perhaps even rocks.

More evidence for radiobiologically sound data is rapidly accumulating, e.g. for radon, with the overwhelming smoking effect, indicating no additional risk but perhaps hormesis below 600-1000 Bq/m³ suggesting a practical threshold not lower than 600-1000 Bq/m³. Large differences between the conditions in mines and homes make it impossible to extrapolate from miner to residential data. Concerning low-LET low dose-rate external radiation data ranging over many generations in several high-dose areas show no negative, in some cases even biopositive effects. Nevertheless, the unfortunate controversy between authorities and scientists is likely to continue for years.

RESPONSES TO LOW DOSES OF IONIZING RADIATION IN BIOLOGICAL SYSTEMS

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Biological tissues operate through cells expressing and being embedded in a signaling network. This assures coordinated cell function in the face of constant exposure to an array of potentially toxic agents from the environment and endogenously from metabolism. Tissues are indeed complex adaptive systems.

Regarding low-dose tissue irradiation, 1) absorbed tissue dose is replaced by the sum of energy deposited per track event, hit, in a cell-equivalent tissue micromass, i.e., of microdoses, per number of exposed micromasses, with cell-dose being a multiple of microdose-hits; and 2) tissue effects arise from all damaging and protective cellular responses per microdose-hit over all microdose-hits from a given radiation quality in the exposed micromasses.

The probability of DNA damage per low-LET type microdose-hit is extremely small; it increases proportional with the number of microdose-hits. Delayed appearing temporary adaptive protection, AP, is readily measured at small but not large numbers of low-LET microdose-hits per exposed micromasses in many species and cell systems. AP may last from days to weeks operating mainly against non-radiogenic, largely endogenous DNA damage, which occurs abundantly and constantly compared to damage caused by rare microdose-hits per micromass from background radiation. AP involves a) induced detoxification of reactive oxygen species, b) enhanced rate of DNA repair, c) enhanced removal of damaged cells by apoptosis followed by normal cell replacement, and d) stimulation of immune response. These adaptive protective responses are associated with corresponding changes in gene expression. The balance between damage and protection favors protection at low cell-doses and damage at high cell-doses. Bystander effects from high-dosed cells to non-irradiated neighboring cells appear to include both damage and protection.

A model based on the above dual response pattern predicts that at low doses and dose rates the linear-no-threshold hypothesis of radiation-induced cancer is invalid in favor of a function that includes both linear and non-linear terms.

RADIATION-INDUCED CHANGE IN CELL PROLIFERATION AND ITS NEUROENDOCRINE REGULATION: DOSE-RESPONSE RELATIONSHIP AND PATHOPHYSIOLOGICAL IMPLICATIONS

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Cellular activities are regulated by intracellular signals initiated by stimulation from external and internal environment. Different signal pathways are involved in the initiation of different cellular functions. In connection with cell proliferation in response to mitogenic stimulation the dose-effect relationship of the magnitude of ^{3}H-TdR incorporation into lymphocytes after exposure to different concentrations of Con A showed an inverted U-shaped curve in the concentration range of 2~30 μg/ml. When a suboptimal dose of Con A (5 μg/ml) was chosen, the stimulatory effect of whole-body X-irradiation with low dose (0.075 Gy) and suppressive effect of high dose (2 Gy) on Con A-induced lymphocyte proliferation have been repeatedly demonstrated. When different concentrations of corticosterone ranging from 0.1 to 100 μmol/L were added to the Con A-stimulated lymphocytes, low concentration stimulation and high concentration suppression of lymphocyte proliferation were observed. In the presence of 5 pM/L (subphysiological concentration) of corticosterone the proliferation of thymocytes and splenic T cells in response to Con A was further up-regulated after low dose radiation. Low dose radiation (0.075 Gy) caused lowering of serum ACTH and corticosterone concentration as well as down-regulation of hypothalamic *POMC* transcription. In the present paper it is intended to show that multiple neurohormonal factors, including the hypothalamic-pituitary-adrenocortical axis, pineal gland and catelcolamines, are involved in the stimulation of immune response induced by low dose ionizing radiation. These data illustrate the complex nature of the interrelationship between the intracellular signaling and the neuroendocrine regulation after whole-body irradiation and give further support to the phenomenon of low dose stimulation and high dose suppression of cell proliferation related to complex systemic regulation and intracellular signaling evoked by different doses of ionizing radiation.

LOW-DOSE RADIATION AND GENOTOXIC CHEMICALS PROTECT AGAINST STOCHASTIC BIOLOGICAL EFFECTS

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The linear nonthreshold (LNT) model plays a central role in low-dose risk assessment for stochastic biological effects. With the LNT model, any exposure to radiation or a genotoxic chemical is assumed to increase one's risk of problematic, non-lethal mutations and cancer (both are stochastic effects). The risk increases linearly with dose. Using the LNT model, others have "calculated" tens of thousands of deaths related to environmental exposure to radioactive material from nuclear accidents (e.g., Chernobyl) and nuclear weapons fallout. Here, we present a mechanistic model for low-dose-radiation- or genotoxic-chemical-induced, stochastic effects (mutations and neoplastic transformations) that leads to a nonlinear relationship between the risk and dose. We provide experimental evidence (supported by our mechanistic model) that low-dose radiation and genotoxic chemicals such as ethylene oxide (a prototypic alkylating agent) can turn on a protective mechanism that leads to a reduction in the risks of stochastic effects. We attribute the protection to a bystander apoptotic effect whereby normal cells (among the large number at risk) hit by the genotoxic agent of interest initiate intracellular signaling that causes some of the already existing problematic bystander cells (*Hprt* mutants, neoplastically transformed cells, etc.) to selectively undergo apoptosis. We speculate, partly based on work of others, that such protection may also be induced by low doses to operate on existing cancer cells and may be amplified by apoptosis-inducing agents such as dietary isothiocyanates and other genotoxic chemicals. If corroborated, this model could lead to novel, low-dose cancer therapy procedures. Because neoplastic transformation is considered to be a necessary early step in cancer induction, our results related to low-dose-induced protection are interpreted to indicate that dose thresholds may exist for excess cancer induction by radiation and genotoxic chemicals. (Research supported by the U. S. Department of Energy, Offices of Science and Environmental Management).

LOW DOSE RADIATION HEALTH AND MEDICAL BENEFITS: A CENTURY OF HARD DATA AND SOFT SCIENCE

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In 1896, the year following Roentgen's description of the construction of x-ray tubes and the results of x-rays, low-dose exposures of animals and humans showed that the effects of stimulating immune responses to prevent and cure infections and inflammations. These results were confirmed in studies and comprehensive reviews of the results of low vs. high dose effects on physiology in animals and plants in the two decades following the discovery of x-rays, including the application of radium. In the 1920s, positive immune responses to low doses were shown to also prevent and cure cancer. Medical applications applied the beneficial effects to treat infections and inflammatory diseases through the first half of the 20th century. Such applications continue into the 21st Century. However, the advent of drugs, especially antibiotics, caused LDR therapies to be marginalized. Research and documentation in the second half of the 20th century applied new biological tools in cellular and molecular biology to prove the immunological efficacy and application of LDR to prevent and treat diseases, including cancer. In addition, evidence of LDR stimulation of biophotons and biogenic radiation further demonstrates that LDR is essential to life. These effects are inconsistent with the premise that presumes that "DNA damage" is relevant to evaluating radiation health effects. Research measuring in vitro responses can help elucidate some mechanisms, but it is not relevant to assess LDR effects on health. However, current government reviews and agency programs that direct research funds discount the relevant evidence and prevent medical applications and clinical trials under conditions that would be readily undertaken for drug protocols with equivalent scientific foundation, and to misdirect research. Therefore, cost-effective LDR medical applications are precluded in favor of costly and less effective drug therapies, and massive programs and costs for "radiation protection" are justified.

SESSION III: CHEMICAL CARCINOGENESIS

DOSE-RESPONSE CURVES IN CHEMICAL CARCINOGENESIS

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DETOXICATION STRATEGY OF EPOXIDE HYDROLASE – THE BASIS FOR A NOVEL THRESHOLD FOR DEFINABLE GENOTOXIC CARCINOGENS

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DOSE-RESPONSE CURVES IN CHEMICAL CARCINOGENESIS

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Extrapolation from studies of chemical carcinogenicity in rodents at high doses to humans at the typically low doses to which we are exposed has been one of the most controversial issues in toxicology. The Linearized Multistage is currently the most widely accepted model for this extrapolation. That model, however, has several serious flaws. Among these are that it ***assumes*** that there is zero tumor production only at zero dose, the doses are evaluated on a linear scale, and it does not fully evaluate the shape of the dose-response curve in the animal experiments. Other plots, e.g., log-log, reciprocals, etc., have been equally controversial and without a sound scientific basis. Recent re-evaluations of several prominent studies, e.g., the ED01 study, N-nitrosodiethylamine, etc. (Waddell 2002, 2003a, 2003b) unequivocally demonstrate thresholds for carcinogenicity when the dose-response curves for animal studies done at high doses are calculated according to fundamental principles of chemistry (Waddell and Bates, 1969; Rozman, et al. 1996). These re-evaluations agree, at least, with a direct linear correlation between percent tumors and the logarithm of the dose in all of the approximately 50 studies re-examined to date. In each of these, the thresholds are only slightly below the maximum tolerated doses. This observation now places these high-dose experiments in animals in a category completely removed from the exposures typically encountered by humans. This truly raises the issue of their relevance and what effect, if any, exposures to these compounds at low doses have on humans. Other examples of disagreement between previous extrapolations from animal studies and results from epidemiological studies have been published (Waddell, 1993, 1996, 2003c). It is suggested that the actual shape of the dose-response curve for each study should be examined according to scientific principles; this may allow discernment for thresholds, "U" or "J" shaped curves, etc. that may not otherwise be noted. An example of the need to examine more closely human studies is the report by Tuyns (1983) of esophageal cancer in non-smoking drinkers. This study was interpreted to show a steadily increasing relative risk for cancer with increasing consumption of alcohol (IARC, 1988). However, in that study, drinkers of up to 40 grams per day were the reference group. If, however, true non-drinkers were used as the reference group, the dose-response curve is clearly "J" shaped.

DETOXIFICATION STRATEGY OF EPOXIDE HYDROLASE – THE BASIS FOR A NOVEL THRESHOLD FOR DEFINABLE GENOTOXIC CARCINOGENS

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From our recent work on the three-dimensional structure of epoxide hydrolases we theoretically deduced the likelihood of a two step catalytic mechanism which we and others have subsequently experimentally confirmed. Analysis of the rate of the two steps by us and by others show that the first step – responsible for removal of the reactive epoxide from the system – works extraordinarily fast, sucking up the epoxide like a sponge. Regeneration of the free enzyme (the second step of the catalytic mechanism) is slow. This becomes a toxicological problem only at doses of the epoxide which titrate the enzyme out. Our genotoxicity work shows that indeed this generates a practical threshold below which no genotoxicity is observed. This shows that – contrary to old dogma – practical thresholds exist for definable genotoxic carcinogens.

SESSION IV: BIOMEDICAL

THE TREATMENT OF CHRONIC PROSTATITIS WITH LOW LEVEL CHORIONIC GONADOTROPIN

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NON-LINEAR DOSE-RESPONSE EFFECTS OF NEUROSTEROIDS ON BRAIN PLASTICITY AND MEMORY

David M. Diamond, University of South Florida, and Veterans Hospital, Tampa, Florida

POSSIBLE CLINICAL IMPLICATIONS OF HORMESIS

Wayne Jonas, Samueli Institute, Bethesda, MD

BIPHASIC AND U-SHAPED OPIOID DOSE-RESPONSES IN THE IMMUNE SYSTEM

Burt M. Sharp, University of Tennessee, Memphis, TN

MOLECULAR MECHANISMS OF ANTI-AGING EFFECTS OF MILD HEAT STRESS ON HUMAN CELLS

Dr. Suresh I.S. Rattan, University of Aarhus, Denmark

BIPHASIC RESPONSE OF CIPROFLOXACIN IN HUMAN FIBROBLAST CELL CULTURES

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THE TREATMENT OF CHRONIC PROSTATITIS WITH LOW LEVEL CHORIONIC GONADOTROPIN

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ML-04A, a proprietary sublingual formulation of human Chorionic Gonadotropin (hCG), is an investigational anti-tumor signaling agent. A clinical investigational study for this molecule with the objective to assess the efficacy of 2 Units of ML-04a give 4 times per as a sublingual drop, in improving the clinical symptoms of prostatitis as defined by the NIH chronic pelvic pain syndrome index (NIH-CPSI) during the 12 week treatment period. Human chorionic gonadotropin has been approved by the FDA and marketed for many years. It is typically administered in thousands of units as an injectable substance for induction of ovulation or puberty and has an excellent safety record. Normal endogenous hCG in the adult male appears to regulate normal homeostasis of the prostate. The receptor for hCG has a very low capacity and a very high affinity so that small changes in blood level may induce changes in function. In experimental conditions, hCG induces apoptosis and cytokine changes at low doses but not high doses. Therefore, administering very small levels of hCG to patients prostatitis may function to restore normal function of the prostate and reduce inflammatory and immune components of the disease resulting in a reduction of the irritative and pain symptoms.

NON-LINEAR DOSE-RESPONSE EFFECTS OF NEUROSTEROIDS ON BRAIN PLASTICITY AND MEMORY

***David M. Diamond**, Departments of Psychology and Pharmacology, University of South Florida, and Medical Research Service, Veterans Hospital, Tampa, Florida*

Research conducted largely in the past two decades has shown that the brain can synthesize hormones, *de novo*. These hormones, referred to collectively as neurosteroids, can exert profound effects on brain activity and behavior. It is known that neurosteroids can influence memory and synaptic plasticity, i.e., the changes in the brain that underlie learning and memory. However, the literature is inconsistent, and questions remain as to the effectiveness of neurosteroid administration on cognition and health. My work has examined the effects of administration of one type of neurosteroid, dehydroepiandrosterone (DHEA), on memory and brain plasticity. We have studied the influence of DHEA on the hippocampus, a temporal lobe structure known to be involved in specific forms of memory. Rats were administered a broad range of doses of DHEA, and the effects of the hormone on plasticity in the hippocampus and memory were studied. We found in physiological and cognitive studies that DHEA administration produced a U-shaped dose response function, with intermediate doses producing maximal effects. Proponents of DHEA administration as a cognitive enhancer and as an anti-aging medication should take the non-linear dose-response functions of DHEA into account.

BIPHASIC AND U-SHAPED OPIOID DOSE-RESPONSES IN THE IMMUNE SYSTEM

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Opiate alkyloids and opioid peptides are immunomodulatory, exerting direct effects on proliferation, cytokine production, chemotaxis and intracellular signaling by cells involved in host defense. These cells inducibly express opioid receptors (ORs), encoded by the mu, delta, and kappa OR genes originally described in neuronal tissues. Biphasic and/or U-shaped dose-response relationships are often characteristic of the immunomodulatory actions of opioids. Several examples, which utilize different cell types and dependent variables, will be presented. Thymocytes are progenitors of mature T-cells, which are pivotal in cell-mediated immunity. The $CD4^+$ subset of thymic T-cells expresses transcripts for proenkephalin A (PEA), the precursor to methionine enkephalin which binds to delta ORs. Concanavalin-A-induced thymocyte proliferation and PEA expression were biphasically modulated by pretreatment with deltorphin, a synthetic delta OR agonist; 10^{-14} M was maximally inhibitory to proliferation and stimulatory to PEA expression, whereas 10^{-8} M had opposite effects on each parameter. In addition, naltrindole, a delta OR antagonist, itself enhanced the spontaneous proliferation of both fetal and mature thymocytes, with maximal effects at 10^{-12} M and none at $>10^{-8}$ M. Thus, endogenous enkephalins modulate both their own expression and thymocyte proliferation. Other studies have shown that two delta OR agonists, deltorphin and DAME, each affected anti-CD3-driven interleukin-2 secretion by purified splenic $CD4^+$ T-cells. DAME showed a U-shaped profile and deltorphin had biphasic effects. Lastly, delta OR agonists (SNC-80 and deltorphin) inhibited human immunodeficiency virus-1 (HIV-1) p24 antigen production, an index of HIV expression, by both normal human peripheral blood $CD4^+$ T-cells and a Jurkat T-cell line, which over-expressed delta ORs. The delta OR agonists showed U-shaped dose-dependent inhibition of p24 production, with maximal effects at approximately 10^{-11} M and none at 10^{-6} M. In summary, delta opioid agonists have complex dose-dependent immunomodulatory effects on multiple parameters of T-cell function.

MOLECULAR MECHANISMS OF ANTI-AGING EFFECTS OF MILD HEAT STRESS ON HUMAN CELLS

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In a series of experimental studies we have shown that repetitive mild heat stress has anti-aging effects on growth and various other cellular and biochemical characteristics of human skin fibroblasts undergoing aging in vitro. We have reported the hormetic effects of repeated challenge at the levels of maintenance of stress protein profile, reduction in the accumulation of oxidatively and glycoxidatively damaged proteins, stimulation of the proteasomal activities for the degradation of abnormal proteins, improved cellular resistance to ethanol, hydrogen peroxide and ultraviolet-B rays, and enhanced levels of various antioxidant enzymes. We are now undertaking detailed analysis of the signal transduction pathways in order to determine alterations in the phosphorylation and dephosphorylation states of ER-, JN- and MAP-kinases as a measure of cellular responsiveness to mild and severe heat stress. Furthermore, we are also undertaking comparative studies using non-aging immortal cell lines, such as SV40-transformed human fibroblasts, spontaneous osteosarcoma cells and telomerase-immortalised human bone marrow cells for establishing differences in normal and cancerous cells with respect to their responsiveness to mild and severe stresses.

BIPHASIC RESPONSE OF CIPROFLOXACIN IN HUMAN FIBROBLAST CELL CULTURES

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In order to investigate the possibility of the involvement of an oxidative stress induction in the mechanism of previously reported cytotoxic effect of quinolone antibiotics, we examined the viability of human fibroblast cells exposed to ciprofloxacin (CPFX), and measured the levels of lipid peroxidation, GSH, and the activities of the antioxidant enzymes CAT, SOD, GPX. The data showed that the effect of CPFX on the viability of cells, as determined by neutral red uptake assay, was time dependent, and the dose-response relation was biphasic. Cytotoxicity was not observed in the concentration range of 0.0129-0.387 mM CPFX when the cells were incubated for 24 h. In contrast, lower concentrations (0.0129 and 0.032 mM) of CPFX increased the cell survival in all incubation periods tested. Marked decreases on the viability of fibroblasts were observed at concentrations 0.129 and 0.194 mM, and ≥ 0.129 mM, following 48 and 72 h exposure, respectively ($p < 0.05$). However, when the cells are exposed to > 0.194 mM CPFX for 48 h, no cytotoxicity was observed. By exposing of fibroblast cultures to 0.194 mM CPFX for 48 h, an induction of lipid peroxidation enhancement, and a marked decrease in intracellular GSH was observed. Vitamin E pretreatment of the cells lowered the level of lipid peroxidation, increased the total GSH content, and provided significant protection against CPFX-induced cytotoxicity. The biphasic effect of CPFX possibly resulted from the complex dose-dependent relationships between reactive oxygen species (ROS), cell proliferation and cell viability. It was previously reported, in fact, for several cell models that ROS exert a biphasic effect on cell growth. Furthermore, cultured fibroblasts release their own free radicals, the inhibition of endogenous ROS inhibit the fibroblast cell proliferation, whereas the effects of exogenous ROS are biphasic.

SESSION V: HIGH PROFILE TOXIC SUBSTANCES AND THE NON-LINEAR FEATURES OF THEIR DOSE RESPONSE RELATIONSHIPS

ASBESTOS: NON-LINEAR DOSE RESPONSE RELATIONSHIPS IN IN VITRO ASSAYS AND INHALATION EXPERIMENTS

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THE PARTICULATE AIR POLLUTION CONTROVERSY

Robert F. Phalen, University of California, Irvine, CA

MECHANISTIC MODEL PREDICTS LOW-DOSE NONLINEARITY OF LIVER TUMOR RISK IN MICE FED FUMONISIN B_1

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DIOXIN

Thomas Starr, TBS Associates, Raleigh, NC

THE CHLOROFORM SAGA: SCIENCE TRUMPS POLICY?

Jay Goodman, Michigan State University, East Lansing, MI

JUSTIFICATION, APPLICATION AND IMPLICATION OF PRESUMED LINEARITY FOR DIOXIN AND DIOXIN-LIKE COMPOUNDS

John D. Schell, BBL Sciences, Tallahassee, FL

NON-LINEAR DOSE-RESPONSE RELATIONSHIPS IN ENDOCRINE DISRUPTION

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ASBESTOS: NON-LINEAR DOSE RESPONSE RELATIONSHIPS IN IN VITRO ASSAYS AND INHALATION EXPERIMENTS

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'Asbestos' is a group of naturally occurring mineral fibers which are associated in occupational settings with increased risks of malignant mesothelioma (MM), lung cancers, and pulmonary fibosis (asbestosis). The six recognized types of asbestos fibers (chrysotile, crocidolite, amosite, tremolite, anthophyllite and actinolite) are different chemically and physically and may have different dose-response relationships in the development of various asbestos-associated diseases. For example, epidemiologic and lung fiber content studies suggest that the pathogenic potential and durability of crocidolite ('blue' asbestos mined primarily in South African and Western Australia) is much greater than chrysotile asbestos ('white' asbestos mined in North America) in the causation of human MM. We have used isolated mesothelial cells, the target cells of MM, as well as epithelial cells of the lung, the target cells of lung cancers, *in vitro* to elucidate the dose-response relationships in expression of early response protooncogenes andother genes critical to cell proliferation and malignant transformation in cells exposed to crocidolite and chrysotile asbestos, as well as a number of nonpathogenic fibers and particles. These studies reveal distinct dose-response patterns with different types of asbestos, suggesting a threshold for effects of chrysotile both in *in vitro* studies and inhalation experiments. The different patterns of gene expression have been confirmed in lungs of rats exposed by inhalation to these types of asbestos. Experiments also suggest No Observed Adverse Effect Levels (NOELs) after evaluation of lung injury, inflammation and fibrosis at lower concentrations of both types of asbestos. Supported by grants from NIEHS and NHLBI.

THE PARTICULATE AIR POLLUTION CONTROVERSY

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Epidemiology studies of urban particulate air pollution (particulate matter, PM) stimulated debate, new air regulations, litigation, and a massive worldwide research effort. The epidemiology studies reported weak (but statistically significant) associations between very small daily increments in PM levels and adverse human health measures, including mortality. When the risk factors associated with PM variations in U.S. cities were multiplied by the populations, tens of thousands of annual deaths were predicted nationwide. Although the meaning of these findings was unclear, the mandate of the U.S. EPA, and litigation pressure, prompted new National Ambient Air Quality Standards (NAAQS) for PM. The substantial economic implications and scientific uncertainties surrounding the regulations stimulated unsuccessful legal challenges and the launching of a massive worldwide research effort.

The scientific issues related to the PM controversy are numerous and challenging. The meaning of epidemiology associations based on increments (as opposed to levels) of PM is not obvious. In addition, PM is chemically nonspecific, and it is unclear just how tiny amounts of inhaled particulate mass could be deadly. The ecologic nature of the epidemiology associations, which were based on crude area air monitors, generates questions such as, “Who was affected and by what mechanism(s)?” The ongoing coordinated research effort aims to clarify the uncertainties by integrating information from the areas of epidemiology, toxicology, clinical research and atmospheric science. However, whether such an effort will succeed is unclear unless more fundamental issues are also addressed.

The PM controversy is a case study on how science and environmental regulation are related. Many issues arise, including: the value of establishing biological plausibility before associations are accepted as causal; the relevance of economic and health tradeoffs to setting NAAQS; and the effect on health of accelerated abatement actions.

MECHANISTIC MODEL PREDICTS LOW-DOSE NONLINEARITY OF LIVER TUMOR RISK IN MICE FED FUMONISIN B_1

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Fumonisin B_1 is a naturally occurring mycotoxin produced by various *Fusarium* species of molds. It is found in corn and corn-based food products consumed by humans, and in animal feeds. Fumonisin B_1 is highly toxic to horses and pigs, is carcinogenic in rodents and may be linked to esophageal cancer in humans. A two-year bioassay with rats and mice was conducted at the National Center for Toxicological Research under the National Toxicology Program to characterize the risk of toxicity and carcinogenicity from consumption of food containing fumonisin B_1. To enable the investigation of toxic mechanisms, the bioassay included ancillary studies of cell proliferation and apoptosis, and of sphingolipid metabolism in the two target organs, liver and kidney. A two-stage, clonal-expansion model of liver tumor risk in mice was developed based on the hypothesis that fumonisin B_1 is not genotoxic, but rather causes cancer through the disruption of sphingolipid metabolism. This disruption causes an increase in apoptosis, in response to which cells proliferate to compensate for reduced tissue mass. The resulting differential increase in the number of pre-neoplastic cells at risk of mutation during cell division leads to an increase in the incidence of tumors. The two-year liver tumor incidences predicted by the model using only data from the ancillary studies were overlaid with the actual two-year observed incidences. The predictions were in line with the tumor data, indicating no risk at low doses (even a possible hormetic effect) and high risk at high doses in females, as well as a complete absence of a dose-response in males. The model's results provide scientific support and justification for FDA's low-ppm guidance levels in corn products, which are significantly higher than would be obtained using linear extrapolation, the method most often used for genotoxic carcinogens. The 2001 WHO document on the safety evaluation of mycotoxins in food contains an extensive discussion of the implementation of this mechanistic model in its characterization of the dose-response relationship for cancer.

DIOXIN

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While some scientists and regulatory agencies have concluded that the normal human diet may be responsible for as many as 20,000 additional cancer deaths per year in the United States due to its contamination with dioxin-like compounds, others have concluded that there is no increased risk of cancer mortality whatsoever from this ubiquitous background exposure. How can different investigators reach such markedly different conclusions from similar analyses of essentially the same data for workers exposed occupationally? The answer lies in different choices for a dose metric, different assumptions regarding the elimination half-life for TCDD in humans, different assumptions regarding the impact on potential risk of the most recent period of exposure, and whether or not extrapolations are made from the potential risks posed solely by TCDD exposure to those posed by exposure to any and all dioxin-like compounds. A final resolution of these disparate conclusions will require detailed information on exposure to both direct-acting carcinogens and TCDD in the workplace as well as development of a dose-response model that incorporates TCDD's well-established characteristics as a cancer promoter.

THE CHLOROFORM SAGA: SCIENCE TRUMPS POLICY?

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Chlorination of drinking water represents one of the most significant advances in public health protection. However, chloroform, a by-product of chlorination, is carcinogenic to rodents. Based upon this, using a risk assessment that relied upon a linear extrapolation of tumor data, i.e., a default, no threshold assumption, the U. S. Environmental Protection Agency (EPA) categorized chloroform as a potential human carcinogen. It is instructive to reflect upon the fact that dose influences mechanism, e.g., what happens at high doses does not necessarily occur at low doses (Goodman, 1998). An Expert Panel (JIG was a member) convened by the International Life Sciences Institute, Health and Environmental Sciences Institute (ILSI Panel) reviewed the extensive data base on chloroform and concluded that chloroform carcinogenicity occurs by a secondary mechanism, i.e., it is a direct consequence of tissue injury from reactive, non-mutagenic metabolites, and that a nonlinear, i.e., threshold-exhibiting, approach is appropriate for risk assessment (Andersen et al., 2000; ILSI, 1997).

Based, in part, upon the ILSI Panel's report, in March 1998 EPA proposed a threshold-based approach in setting a drinking water standard for chloroform (EPA, 1998a). However, remarkably, in December 1998 EPA published a final rule in which an MCLG (maximum contaminant level goal) of zero was promulgated for chloroform (EPA, 1998b), based upon a linear, no-threshold, default approach. It is important to understand that the Agency's scientists who drafted the March 1998 chloroform risk assessment (EPA, 1998a) were correct and the problem arose when the Agency's administrators issued their non-science-based final rule (EPA, 1998b). A lawsuit was filed and on March 31, 2000 the United States Court of Appeals for the District of Columbia, concluded that EPA violated its statutory mandate to use the "best available" [scientific] evidence when implementing the provisions of the Safe Drinking Water Act (http://pacer.cadc.uscourts.gov/common/opinions/200003/98-1627a.txt). The Court indicated that EPA had a mandate to use the best available evidence when implementing the provisions of the Safe Drinking Water Act and stated "Finding the Agency's December 1998 rule adopting a zero MCLG for chloroform to be arbitrary and capricious and in excess of statutory authority ... we vacate the rule." Indeed, the Court made the correct decision. However, it is unfortunate that a Court had to intervene to advance science-based risk assessment. EPA is currently "considering" a new drinking water standard for chloroform.

It is essential that we continue to work with and support EPA's scientists. Furthermore, we need to understand that adherence to default approaches to risk assessment when a persuasive body of scientific data to the contrary is available represents <u>failure</u> and detracts from the credibility of toxicological sciences (Conolly et al., 1999).

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JUSTIFICATION, APPLICATION AND IMPLICATION OF PRESUMED LINEARITY FOR DIOXIN AND DIOXIN-LIKE COMPOUNDS

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The group of chemicals collectively referred to as "dioxin and dioxin-like compounds" are the focus of not only intense research activities, but also represent the "chemicals of primary concern" at some of the largest Superfund sites. In the assessment phase at these sites, linearity of the dose-response relationship for the carcinogenic potential of these compounds is explicitly assumed. This "presumed linearity" has significant influence on the public's perception of impacts these compounds have on community health. The justification for this theory is found in the historical "presumed linearity," a policy decision based in part on the adoption of the precautionary principal, even though theoretical and empirical evidence no longer supports this premise. Neither experimental data obtained from animal studies, nor epidemiological data from heavily exposed populations, confirm linearity of the dose-response relationship for carcinogenic effects of dioxin and dioxin-like compounds. The application of the theory of linearity can be found in the default assumption used to derived toxicity factors required for quantitative risk assessments at Superfund sites. The purpose of this exercise is to identify "unacceptable" health risks, and develop cleanup levels that are presumed to be within the acceptable risk range. The output of these assessments are theoretical risk estimates perceived by the general public, most regulators, and even some scientists as having some degree of precision and reality. The implication of presumed linearity, and this false sense of precision, can be found in the extraordinary impact on the regional and national economy associated with the cleanup of large, moderately contaminated sites. Remediation of high concentrations near the source (i.e., source control) is often warranted and effective at halting continual distribution of these compounds. However, presumptive linearity drives cleanup levels to such low concentrations that ultimately large areas require remedies that are costly but have no true risk benefit.

NON-LINEAR DOSE-RESPONSE RELATIONSHIPS IN ENDOCRINE DISRUPTION

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The study of endocrine disruption has been delayed pending resolution of the claim that effects can be seen for hormonally active chemicals below the no effect level for the recognised adverse endocrine toxicities they may produce (NOAEL). This is separate from the demonstrated ability of some endocrine disruptors to elicit dual endocrine effects whose overall dose-response in non-linear. It may also be distinct from the phenomenon of hormesis. Added to this complexity is the probability that future toxicogenomic studies may reveal changes in the levels of mRNAs associated with an adverse endocrine effect, but occurring at doses below the NOAEL. Examples from the literature, and from our own studies, will be used to explore these several uncertainties.

SESSION VI: TOXICOLOGY

NONLINEARITY IN THE IQ-BLOOD LEAD RELATION: REDEFINING LOW LEVEL EXPOSURE

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NON-LINEAR DOSE-RESPONSE RELATIONSHIPS IN EXPERIMENTAL NEUROTOXICOLOGY

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NONLINEAR LOW-DOSE HEMATOTOXICITY

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NONLINEARITY IN THE IQ–BLOOD LEAD RELATION: REDEFINING LOW LEVEL EXPOSURE

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Scientific thinking and public health policy on the neurobehavioral effects of low-level lead exposure have been guided primarily by linear extrapolation of findings from children with blood lead (PbB) levels > 10 μg/dL, the current CDC and WHO "level of concern." Although a PbB concentration of 10 μg/dL is currently considered to be low, analysis of ancient bone samples estimate that it is 300–500 times greater than that of preindustrial humans. A review of the literature suggests that estimating the neurobehavioral effects of PbBs below 10 μg/dL from samples of children whose PbBs are primarily in the 10–30 μg/dL range is unwarranted. The current longitudinal study assessed children's lifetime average PbB from blood samples taken at 6, 12, 18, and 24 months, then yearly through age 5. Most children's PbBs never exceeded 10 μg/dL. The Stanford-Binet Intelligence Scales were administered at ages 3 and 5 years. Statistical methods included covariate-adjusted parametric and semiparametric mixed models. Both types of analysis indicated that the IQ–PbB relation is nonlinear and that the slope of the estimated curve is steeper at lower as opposed to higher PbBs. Estimated by penalized spline smoothing, the average IQs of children with PbBs of 10 μg/dL are 7.4 points lower than for children with PbBs of 1 μg/dL. Effect sizes are similar for the 3- and 5-year IQ assessments independently. Furthermore, the estimated curve indicates that the average IQs of children with PbBs of 30 μg/dL are only 2.5 points lower than for children with PbBs of 10 μg/dL, similar to estimates from recent meta-analyses of pediatric lead exposure studies. These results illustrate the importance of investigating exposure levels below those commonly considered harmful, the benefits of nonparametric methods to model exposure–response functions, and the need for a redefinition of low-level lead exposure.

NON-LINEAR DOSE-RESPONSE RELATIONSHIPS IN EXPERIMENTAL NEUROTOXICOLOGY

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Nervous tissue is the target for many toxic substances which can damage a range of structural and metabolic capacities. The toxic effects also reflect the regional and cellular heterogeneity of the nervous system. Emerging data, largely obtained from in vitro studies, provide good evidence that many of the toxic responses are non-linear, with low-dose increases in protection. These non-linear capacities are a prominent feature of astrocytes. This population of CNS glial cells, and several analogous lines of glioma cells, have been studied extensively in culture systems. The dose-responses to different toxicants, including metals, has been assessed by several types of markers (including structural proteins, antioxidant protective systems and energy metabolism). The end-point responses frequently exhibited bi-phasic patterns, with low-dose enhancement of indicator values opposite to those occurring with higher, damaging concentrations of toxicants. The low-dose changes occurred at similar levels of toxicants to those which initiate astrocyte activation. Astrocyte activation occurs both in vivo and in vitro and involves extensive alterations in cell phenotype, with upregulation of a large number of molecules, including those controlling the protective systems. We conclude that astrocytes in culture can respond to low-doses of toxicant with increased protective capacities. Substantial indirect evidence indicates that similar phenomena may occur in the intact nervous system.

NONLINEAR LOW-DOSE HEMATOTOXICITY

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Epidemiological investigations of low-dose occupational exposures to benzene and/or mixtures of volatile organic compounds (VOCs) and risks of neoplasms (especially acute myeloid leukemias and non-Hodgkins lymphomas) have produced inconsistent results. Some authors (e.g., Paxton, 1996; Schnatter et al., 1996) have reported apparent exposure concentration thresholds for increased risks; others find a sub-linear or zero dose-response relation (e.g., Crump, 1996; Albin, 2000), and still others descry positive risks from low estimated (but highly uncertain) exposures (Qu et al., 2002; Hayes et al., 2001). To clarify the shapes of low-dose dose-response relations for benzene and VOC mixtures including benzene, we have been developing a mechanistic pharmacokinetic-pharmacodynamic (PBPK/PD) model of the effects of hematotoxins on hematopoietic stem cell populations (e.g., CFU-GM) involved in chemically-induced myelodysplastic syndrome (s-MDS) and acute myeloid leukemia (s-AML). The PD portion of the model, including an experimentally validated feedback-control model of suppression and compensating proliferation of hematopoietic stem cells in response to hematotoxins, has been developed and compared to experimental data in mice, rats, and dogs and to clinical data in humans, using benzene, radiation, and the immunosuppressive agent cyclophosphamide as test compounds. A striking and unexpected feature of the resulting model of bone marrow hematotoxicity is that sufficiently low concentrations of benzene or benzene-containing VOC mixtures are predicted to *reduce* stem cell proliferation, premature recruitment of early stem cells, and resulting risk of s-MDS and s-AML. The prediction of a U-shaped dose-response relation is robust to model uncertainties, but it occurs only below the concentrations used in most experiments. The model successfully explains some past puzzles in published data (e.g., how and why smaller total doses of inhaled benzene can have larger hematotoxic effects if administered as a relatively short, concentrated dose) and may help to interpret the epidemiology of low exposures to benzene and hematotoxic VOC mixtures.

SESSION VII: REGULATORY FORUM ON NON-LINEAR DOSE RESPONSE

LOW DOSE RADIATION HEALTH EFFECTS: REGULATORY FOUNDATIONS

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NON-LINEAR DOSE RESPONSE: GOOD SCIENCE YIELDS EFFECTIVE REGULATION

Matthew S. Bogdanffy, DuPont Haskell Laboratory for Health and Environmental Science, Newark DE

SETTING AMBIENT WATER QUALITY STANDARDS: NEW YORK STATE'S NON-LINEAR APPROACH FOR CARCINOGENS

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LOW DOSE RADIATION HEALTH EFFECTS: REGULATORY FOUNDATIONS

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Papers in "Science" by Pusey (1911) and Richards (1915) summarized the clear evidence of the physiologically stimulating effects of low vs. high radiation doses. In the 1910s-20s, papers by Russ, Mottram, Murphy and others showed that the stimulatory effect of low vs. high radiation doses stimulated instead of suppressed lymphocytes causing protection against tumors and established tumors to regress. Also in the 1920s, in the UK, the radiologists undertook to eliminate the electrical engineers and photographers and other x-ray practitioners in order to put the medical x-ray applications in the hands of the "medical men." As usual in channeling revenues into one's own pocket, the claim was to "protect the public" from the hazards of x-rays. The "medical men" were less knowledgeable about health effects, and more interested in diagnostic imaging and high-dose therapies. Even in using low-dose therapies that stimulated the immune response, there was a lack of patience and a "more is better" mindset. By the 1930s there was growing public use of radiation therapies without "medical prescription." Then in 1932 Eben Byers, a wealthy industrialist socialite died a gruesome death after 3 years of ingesting massive quantities of radium in Radithor elixir. The U.S. FDA got Congress to give them control. On behalf of the "medical men" it promulgated fear and suppressed non-medical use of radiation.

In the 1930s, the ICRP and NCRP were created by the medical establishment, which coincided with development of therapeutic drugs. The FDA undertook a report, under the rubric of the NAS, to "find" that low dose radiation did not have health and medical benefits, despite decades of data and active use in medical applications to the contrary. They found a researcher who failed to find any stimulatory effects in plants (something that high school science fair participants can find using a dental x-ray machine) despite the work of colleagues and substantial literature. These and other review bodies are interlocked and self-perpetuating groups of scientists and non-scientists driven by government funding. Research that refutes the LNT model is routinely terminated. Mainstream researchers avoid such errors. Nevertheless substantial research is produced that explicitly refutes the LNT. Such research is suppressed by the review bodies.

The suppression of evidence, and the suppression of research, is the consistent standard for research funded to support the regulatory agencies, and the conduct of the government review bodies up to the recent NCRP Report 136, which, despite voluminous data and initial NRC direction "to consider all of the data," NCRP failed to do so, producing another highly biased report founded on high dose data and in vitro dose-response to conclude that the LNT is justified. By then, the NRC prevented the NRC reviewers from considering the plain fact that NCRP had not considered the data. Commissioner Dicus was made a member of the ICRP.

Since 1994, the Massachusetts Governor's Advisory Council on Radiation Protection has documented thousands of studies and hundreds of researchers that have documented results that refute the premise that low dose response can be linear. The regulatory agencies and review bodies continue a 75-year commitment to ignore and suppress that evidence. The costs/profits of that commitment and its associated commitment to terrify the public are to extract $100s of billions from the gullible public for zero public health benefit.

NON-LINEAR DOSE RESPONSE: GOOD SCIENCE YIELDS EFFECTIVE REGULATION

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The first regulatory approaches to assessing carcinogen risk were derived from an understanding of the biology of radiation-induced cancer. Mathematical descriptions of these biological processes, coupled with a mandate to protect public health conservatively, produced and entrenched the default assumption of low-dose linearity. Research over the last several decades provides numerous examples of supra- and sub-linear dose response curves, and modes of action that likely have practical thresholds, all of which lead to the conclusion that the default assumption of linearity as it is practiced is probably wrong. More importantly though, the hypothesis of low dose linearity is not testable and therefore the default assumption is at best a policy based on outmoded theory and at worst an impediment to the implementation of scientifically based risk assessments. This brief presentation will illustrate why a harmonized approach to cancer and non-cancer risk assessment is warranted, why appropriate levels of health protection can be accommodated without invoking the contentious default linear assumption, and how new pharmacokinetic and pharmacodynamic information, either chemical-specific or generic, should be used in place of default assumptions.

SETTING AMBIENT WATER QUALITY STANDARDS: NEW YORK STATE'S NON-LINEAR APPROACH FOR CARCINOGENS

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The New York State Department of Environmental Conservation promulgates ambient water quality standards to protect sources of potable water from contamination by toxic chemicals and other substances. Ambient water quality standards are a state program with US EPA oversight, including a federal Clean Water Act requirement for "triennial review." New York's standards are derived according to procedures in state regulation and in conjunction with the New York State Department of Health. Because standards are set at levels much below those that demonstrate effects in laboratory studies, high-to-low dose extrapolations are required. The procedures address both carcinogenic and noncarcinogenic effects. Existing regulations essentially require a linear high-to-low dose extrapolation for carcinogenic effects of a chemical (i.e., there is a finite risk at all doses above zero dose). The regulations also require a non-linear high-to-low dose extrapolation for the non-carcinogenic effects (uncertainty factor approach) of the chemical (i.e., once below the threshold for the effect, the risk at all doses above zero is zero.) New York's ongoing triennial review is addressing both standards and standard-setting procedures. Proposed revisions to the procedures, yet to be formally adopted, would allow greater flexibility and use of a non-linear, uncertainty factor based approach for carcinogenic effects of chemical where warranted. The presentation will focus on the expected revisions to the procedures for carcinogenic effects.

POSTER SESSION

THE INFLUENCE OF LEAD AND MERCURY ON BETA-AMYLOID AGGREGATION AND CYTOTOXICITY
M.D. Basha, University of Rhode Island, Kingston, RI
W. Wei, University of Rhode Island, Kingston, RI
N.H. Zawia, University of Rhode Island, Kingston, RI

EFFECT OF HYDROPEROXIDE AND WATER SPECIMENS OF DIFFERENT COMPOSITION AND PHYSICOCHEMICAL PROPERTIES ON THE STRUCTURE OF MEMBRANES AND ACTIVITY OF MEMBRANE ENZYMES
Elena B. Burlakova, Emanuel Institute of Biochemical Physics, Moscow, Russia
Alexander N. Goloshchapov, Emanuel Institute of Biochemical Physics, Moscow, Russia
Elena M. Molochkina, Emanuel Institute of Biochemical Physics, Moscow, Russia
Lyudmila D. Fatkhulina, Emanuel Institute of Biochemical Physics, Moscow, Russia

HEMATOPOIETIC HORMESIS AND ADAPTIVE RESPONSE INDUCED BY LDR IS LIKELY DUE TO UP-REGULATION OF HEMATOPOIESIS-RELATED CYTOKINES
Guangjun Wang, The First Hospital of Jilin University, PR China
Lu Cai, The First Hospital of Jilin University, PR China and The University of Louisville, KY

METALLOTHIONEIN AS AN ADAPTIVE PROTEIN PREVENTS DIABETES AND ITS TOXICITY
Lu Cai, Department of Medicine, University of Louisville, KY

HORMESIS AT NTP: EVIDENCE OF HORMETIC DOSE RESPONSES IN NTP DOSE-RANGE STUDIES
Edward J. Calabrese, University of Massachusetts, Amherst, MA
Linda A. Baldwin, University of Massachusetts, Amherst, MA

EXPERIMENTAL STUDY OF SUBCHRONIC TOXICITY OF LANTHANUM NITRATE ON LIVER IN RATS
Dong Chen, Jilin University, Changchun, Jilin, P.R. China
Ying Liu, Jilin University, Changchun, Jilin, P.R. China
Yu-Xiu Nie, Jilin University, Changchun, Jilin, P.R. China

THE IMMUNE EFFECTS OF RADIATION OBSERVED FROM THE INCIDENT OF CO-60 CONTAMINATED APARTMENTS IN TAIWAN
W.L. Chen, Nuclear Science & Technology Association,Taipei, Taiwan, ROC
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Health Risks from Fluoridated Water
Myron J. Coplan, Intellequity Technology Services, Natick MA

SECONDARY ULTRAWEAK LUMINESCENCE FROM HUMIC ACIDS INDUCED BY GAMMA RADIATION
Wieslaw Goraczko, Poznan University of Technology, Poznan, Poland
Janusz Slawiñski, Poznan University of Technology, Poznan, Poland

NON-LINEAR DOSE RESPONSE RELATIONSHIPS IN THE DEFINITION OF OCCUPATIONAL EXPOSURE LIMITS
Ivo Iavicoli, Institute of Occupational Health, Università Cattolica del Sacro Cuore, Roma, Italy
Giovanni Carelli, Institute of Occupational Health, Università Cattolica del Sacro Cuore, Roma, Italy

EFFECTS OF LOW-DOSE EXPOSURES TO X-RAYS ON THE NON-SPECIFIC ANTI-TUMOR RESPONSES IN MICE
Aneta Cheda, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Jolanta Wrembel-Wargocka, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Emil Lisiak, Military Institute of Hygiene and Epidemiology, Warsaw, Poland,
Ewa Nowosielska, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Maria Marciniak, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Marek K. Janiak, Military Institute of Hygiene and Epidemiology, Warsaw, Poland

EFFECT OF SINGLE WBI WITH LOW DOSES OF X-RAYS ON THE DEVELOPMENT OF AND BLOOD SUPPLY TO THE PULMONARY TUMOR COLONIES IN MICE
Emil Lisiak, Military Institute of Hygiene and Epidemiology, Warsaw, Poland,
Miroslaw Dziekiewicz, Clinical Hospital of Military Medical University, Warsaw, Poland
Krzysztof W. Zielinski, Military Medical University, Lodz, Poland
Aneta Cheda, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Jolanta Wrembel-Wargocka, Military Institute of Hygiene and Epidemiology, Warsaw, Poland
Sebastian Dominiak, Military Medical University, Lodz, Poland
Marek K. Janiak, Military Institute of Hygiene and Epidemiology, Warsaw, Poland

HETEROGENEOUS EXPOSURE DOSE LEVELS UNABLE TO INDUCE HARMFUL EFFECTS OF LIFE EXPECTANCY AND BLASTOMOGENESIS
Valentina S. Kalistratova, State Research Center of Russia, Moscow, Russia
Lev A. Buldakov, State Research Center of Russia, Moscow, Russia
Petr G. Nisimov, State Research Center of Russia, Moscow, Russia
Irina B. Romanova, State Research Center of Russia, Moscow, Russia

STRESS RESPONSE AND CELLULAR LONGEVITY: THE PROLONGED LIFESPAN OF CUSHING'S-SYNDROME-PATIENTS' FIBROBLASTS
Dimitris Kletsas, National Centre for Scientific Research "Demokritos", Athens, Greece
Harris Pratsinis, National Centre for Scientific Research "Demokritos", Athens, Greece
Irene Zervolea, National Centre for Scientific Research "Demokritos", Athens, Greece
Dimitri Stathakos, National Centre for Scientific Research "Demokritos", Athens, Greece
Fivos Giannakopoulos, Evangelismos Hospital, Athens, Greece
Nikos Thalassinos, Evangelismos Hospital, Athens, Greece
Stylianos Tsagarakis, Evangelismos Hospital, Athens, Greece

HORMETIC EFFECTS AT CLINICAL LEVELS
Marios Kyriazis MD, British Longevity Society, Hemel Hemsptead, UK

SYNERGY – THE EFFECT OF COMBINING NON-LINEAR DOSE PROFILES: THE PREDICTION AND Quantification of the Potentiation of EDTA with Antimicrobials
R. J. W. Lambert, R^2-Scientific,Sharnbrook, Beds, United Kingdom
Stephen P. Denyer, University of Brighton, Brighton, United Kingdom
Geoff W. Hanlon, University of Brighton, Brighton, United Kingdom

EFFECT OF LOW AND VERY LOW DOSES OF SIMPLE PHENOLICS ON PLANT PEROXIDASE ACTIVITY
Elzbieta Malarczyk, Maria Curie-Sklodowska University, Lublin, Poland
Janina Kochmanska-Rdest, Maria Curie-Sklodowska University, Lublin, Poland
Marzanna Pazdzioch-Czochra, Maria Curie-Sklodowska University, Lublin, Poland

THE USE OF STREPTOLYSIN O FOR THE TREATMENT OF SCARS, ADHESIONS AND FIBROSIS
Stephen W. Mamber, Milkhaus Laboratory, Providence, RI
Vit Long, Milkhaus Laboratory, Providence, RI
Ryan G. Rhodes, Milkhaus Laboratory, Providence, RI
Sunthorn Pond-Tor, Milkhaus Laboratory, Providence, RI
Lyn R. Wheeler, Milkhaus Laboratory, Providence, RI
Kellie Fredericks, Milkhaus Laboratory, Providence, RI
Brian Vanscoy, Milkhaus Laboratory, Providence, RI
Jean-Frederic Sauniere, Milkhaus Laboratory, Providence, RI
John McMichael, Milkhaus Laboratory, Providence, RI
Remy Steinschneider, Bio Expertise Technologies, Marseille, France
Jean-Claude Laurent, Bio Expertise Technologies, Marseille, France

THE USE OF LOW DOSE THIMEROSAL FOR THE TREATMENT OF HERPESVIRUS INFECTIONS
Sunthorn Pond-Tor, Milkhaus Laboratory, Inc., Providence, RI
Ryan G. Rhodes, Milkhaus Laboratory, Inc., Providence, RI
Albert E. Dahlberg, Milkhaus Laboratory, Inc., Providence, RI
John McMichael, Milkhaus Laboratory, Inc., Providence, RI

COMPARISON *IN VIVO* STUDY OF GENOTOXIC ACTION OF HIGH VERSUS VERY LOW DOSE-RATE γ-Irradiation
Andreyan N. Osipov, Moscow SIA"Radon", Moscow, Russia
Dmitry Yu. Klokov, Institute of Theoretical and Experimental Biophysics, Moscow Region, Russia
Alexander L. Elakov, Moscow SIA"Radon", Moscow, Russia
Olga M. Rozanova, Institute of Theoretical and Experimental Biophysics, Moscow Region, Russia
Svetlana I. Zaichkina, Institute of Theoretical and Experimental Biophysics, Moscow Region, Russia

EFFECT OF LOW DOSE OF CADMIUM ON TRANSFORMATION OF NORMAL HUMAN PROSTATE CELLS
N.V. Rajeshkumar, Uniformed Services University of the Health Sciences, Bethesda, MD
Jaya P. Gaddipati, Uniformed Services University of the Health Sciences, Bethesda, MD
Jason C. Grove, Uniformed Services University of the Health Sciences, Bethesda, MD
Radha K. Maheshwari, Uniformed Services University of the Health Sciences, Bethesda, MD
Wayne B. Jonas, Samueli Institute for Information Biology, Alexandria, VA

HORMETIC MODULATION OF AGING AND LONGEVITY IN FRUITFLIES
Dr. Suraj P. Sharma, Guru Nanak Dev University, Amritsar, India
Dr. Suresh I.S. Rattan, University of Aarhus, Aarhus, Denmark

ALCOHOL AND BLOOD PRESSURE: A COMPLEX NONLINEAR RELATIONSHIP
Arthur L. Klatsky, MD, Kaiser Permanente Medical Center, Oakland, CA
Natalia V. Udaltsova, PhD, Kaiser Permanente Division of Research, Oakland CA

PARTICULATE MATTER (PM) INCREMENTS MAY NOT BE CAUSAL IN MORTALITY AND MORBIDITY
Peter A. Valberg, Gradient Corporation, Cambridge, MA

EPIDEMIOLOGICAL EVALUATION OF THE THRESHOLD MODEL FOR HEXAVALENT CHROMIUM
Edwin van Wijngaarden, Applied Epidemiology, Inc., Amherst, MA
Rose S. Luippold, Applied Epidemiology, Inc., Amherst, MA
Kenneth A. Mundt, Ph.D., Applied Epidemiology, Inc., Amherst, MA

THE APP PROMOTER RESPONDS TO PB EXPOSURE IN TRANSFECTED PC12 CELLS
W. Wei, University of Rhode Island, Kingston, RI
M.D. Basha, University of Rhode Island, Kingston, RI
N.H. Zawia, University of Rhode Island, Kingston, RI

LOW DOSES GAMMA-RADIATION INDUCE NON-LINEAR DOSE RESPONSE IN MAMMALIAN AND PLANT CELLS
Svetlana I. Zaichkina, Institute of Theoretical and Experimental Biophysics, Moscow Region, Russia
Olga M. Rozanova, Institute of Theoretical and Experimental Biophysics, Moscow Region, Russia
Gella F. Aptikaeva, Institute of Theoretical and Experimental Biophysics, Moscow Region, Russia
Asia Ch. Achmadieva, Institute of Theoretical and Experimental Biophysics, Moscow Region, Russia
D.Ju Klokov, Institute of Theoretical and Experimental Biophysics, Moscow Region, Russia

EFFECT OF MIXED RARE EARTH CHANGLE CROSSING PLACENTA MEMBRANE ON EMBRYO CELL DNA Damage
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THE INFLUENCE OF LEAD AND MERCURY ON BETA-AMYLOID AGGREGATION AND CYTOTOXICITY

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Alzheimer's disease (AD) is a neurodegenerative disease with a substantial medical and societal impact. The "amyloid cascade hypothesis" states that overproduction of the 39-42 amino-acid form of Abeta leads to increased aggregation and deposition of Abeta, an important constituent of senile plaques in the brains of AD patients (reviewed by Selkoe, 1999). The predominately sporadic nature of AD and the occurrence of neurodegenerative processes in the aging brain suggest that the environment may play a role in the development of AD. Lead (Pb) and (Hg) are persistent in the environment and humans are chronically exposed them. A potential mechanism through which these metals could accelerate neurodegeneration is by directly influencing the dynamics of Abeta aggregation and cytotoxicity. We tested the ability of both these metals to induce aggregation and examined the toxicity of the aggregates on PC12 cells, which had been pre-exposed to various concentrations of these metals. We found that nanomolar levels of these metals significantly enhanced the aggregation of Abeta and had a more lethal effect on PC12 cells that had been pre-exposed to these metals. These results suggest that environmental metals may constitute a potential risk factor for the development of neurodegenerative disorders such as AD.

EFFECT OF HYDROPEROXIDE AND WATER SPECIMENS OF DIFFERENT COMPOSITION AND PHYSICOCHEMICAL PROPERTIES ON THE STRUCTURE OF MEMBRANES AND ACTIVITY OF MEMBRANE ENZYMES

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In recent years, attention of researchers has been drawn to the role of active oxygen species in the effects of ultra-low doses of biologically active substances. Supposedly, the effects exerted by ultra-low doses of biologically active substances and exposures to low-level ionizing and non-ionizing radiation are associated, to some extent, with generation of active oxygen species in the reaction medium. We studied the effect of hydroperoxide in the concentration range from 10^{-17} to 10^{-4} M on the activity of AchE, the structure of synaptosomes, and POL in microsomes, along with the effect of specifically treated various water specimens on the structural properties of membranes. Fluidity of the membranes was studied with spin probe and ESR techniques. A nonlinear dependence of the effect on a substance concentration, irradiation dose, and change of sign of the effect was discovered for the range of medium doses. The obtained results were interpreted in the context of an important role of active oxygen species in structurization of water.

HEMATOPOIETIC HORMESIS AND ADAPTIVE RESPONSE INDUCED BY LDR IS LIKELY DUE TO UP-REGULATION OF HEMATOPOIESIS-RELATED CYTOKINES

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We have demonstrated an induction of hormesis and adaptive response in hematopoietic system by low-dose radiation (LDR). In the present study, we further investigated the molecular mechanisms of the hematopoietic hormesis by LDR using cultured mouse progenitor/stem cells *in vitro* to measure the expression of protein and mRNA of GM-CSF, G-CSF and IL-3 with ELISA, slot blot hybridization, *in situ* hybridization and Northern blot methods. The results showed: (1) a hormetic response in hematopoietic system was induced by LDR of 25-100 mGy with an optimal inductive dose of 75 mGy. The count of BFU-E and CFU-GM formation of bone marrow cell reached the peak at 48 hour after LDR. (2) LDR reduced hematopoietic injury caused by high-dose radiation; (3) LDR increased the transcription and expression of GM-CSF and G-CSF genes, reaching a peak level at 9 hour after irradiation by 75mGy; (4) LDR mobilized progenitor/stem cells into the peripheral blood after exposure to 75mGy, and this effect could be further enhanced if LDR was given with co-administration of semi-dose G-CSF. The best scheme was to give LDR to mice at 24 hour after injecting with G-CSF. These results suggest that induction of hematopoietic hormesis and adaptive response by LDR is likely due to up-regulation of hematopoiesis-related cytokines.

METALLOTHIONEIN AS AN ADAPTIVE PROTEIN PREVENTS DIABETES AND ITS TOXICITY

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Metallothionein (MT) is a group of intracellular metal-binding and cysteine-enriched proteins, and highly inducible in various tissues in response to stress. Although it mainly acts as regulator of metal homeostasis such as zinc and copper in tissues, MT also acts as a potent antioxidant and adaptive (or stress) protein to protect cells and tissues from various oxidative stresses. Diabetes affects many Americans and other populations. Diabetes onset and its toxic effect on various organs have been attributed to increased oxidative stress. Studies have shown that zinc-induced or genetically enhanced pancreas MT prevented diabetes induced by chemicals such as streptozotocin and alloxin, and zinc pretreatment also prevented spontaneously developed diabetes. Since diabetic complications are the consequence of the organ's injury caused by diabetic hyperglycemia and hyperlipidemia through oxidative stress, whether MT in non-pancreatic organs also affords preventive effect on diabetic toxicity has been investigated recently. We demonstrated that overexpressed cardiac MT significantly prevented diabetes-induced cardiomyopathy. Likewise, overexpressed hepatic and renal MT also prevented diabetes-induced hepatic and renal toxicity. In addition, we found that as adaptive protein, MT is over-expressed in several organs in response to diabetes. Therefore, biological importance of diabetes-induced MT in the diabetic complications and co-existed other pathogenesis was further explored. It was found that diabetes-induced hepatic and renal MT synthesis was accompanied by a significant prevention of endotoxin-induced hepatic toxicity, and cisplatin-induced renal toxicity. These studies suggest that MT as an adaptive protein can prevent both diabetes onset and its complications or co-existed other pathogenesis. (Supported in part by University of Louisville School of Medicine, Jewish Hospital Research Foundation, American Diabetes Association and Philip Morris External Research Program)

HORMESIS AT NTP: EVIDENCE OF HORMETIC DOSE RESPONSES IN NTP DOSE-RANGE STUDIES

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The National Toxicology Program dose-ranging studies typically employ five dosages and a concurrent control and are conducted for 2- and 13-week exposure periods. Since five doses are employed it suggested the possibilities of the occurrence of sub-NOAEL doses in many of these bioassays and of evaluating the occurrence of hormesis within the NTP bioassay. As a result, 59 environmentally relevant agents in the NTP toxicity database were assessed for their capacity to affect hormetic dose responses for growth as measured by change in weight gain. Hormetic effects were observed with 51 (88%) of the 58 agents evaluated.

EXPERIMENTAL STUDY OF SUBCHRONIC TOXICITY OF LANTHANUM NITRATE ON LIVER IN RATS

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Rare earth elements (REEs) widely exist in nature. China has the richest mineral resources of REEs in the world. Owing to their unique electronic structure and many kinds of fine physiochemical properties, REEs are widely used. There has been rapidly advancing application of REEs in agriculture, forestry, stock raising and medicine since REEs have been discovered to accelerate growth of animals and plants in our country. Some biological effects of REEs such as the absorbance, distribution, deposition in various visceral organs of animals aroused people's extensive attention to the effects of REEs on health. Lanthanum (La) is a light REE, with liver as the chief organ of accumulation of light REEs. In this study, we observed the changes of hepatic fine structure and blood biochemistry in rats after they were fed with different doses of $La(NO_3)_3$.Young Wistar rats were divided into six groups , which were given $La(NO_3)_3$ at 20.0 , 10.0 , 2.0 , 0.2 , $0.1 mg \cdot kg^{-1}$ and the control group with physiological saline, respectively, for six months. Pathological changes of liver were observed by light microscopy and transmission electron microscopy. Glutamic-oxalacetic transaminase (GOT), glutamic-pyruvic transitanase (GPT) , gamma-glutamyl transferase (γ-GT) and alkline phosphatase (ALP) in the serum were measured. The metabolic accumulation of lanthanum in rat liver was investigated by X-ray microanalysis (XMA) and inductively coupled plasma-mass spectrometry (ICP-MS). Results showed no abnormal biochemical changes. In the group of 20.0 $mg \cdot kg^{-1}$ $La(NO_3)_3$, there were lipid droplets and decrease of glycogen in the hepatocytes, denser matrix of the mitochondria, deformation of the nuclei of some hepatocytes with different degrees and infiltration of inflammatory cells in the portal area. The higher the dose, the more the number of bodies contain high electronic dense gravel-like granules and the secondary lysosomes with dense bodies were observed. The content of La in the liver increased regularly with increase in dose and time of administration. The results further proved that low dose $La(NO_3)_3$ produced some specific biologic effects. The result in the group fed $0.1 mg \cdot kg^{-1}$ $La(NO_3)_3$ showed a tendency to hasten synthesis of glycogen and determinately increased growth of animal. This study illustrated the influence of $La(NO_3)_3$ on rat liver at cellular and subcellular levels and it would provide experimental basis for the purpose of setting a reasonable standard for safely utilizing REEs.

THE IMMUNE EFFECTS OF RADIATION OBSERVED FROM THE INCIDENT OF CO-60 CONTAMINATED APARTMENTS IN TAIWAN

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The high dose of acute radiation could harm the blood forming organ, destroying the immune system and resulted deaths to people, such as the dose received in the atomic explosion in Japan. The low dose of acute radiation could also increase the cancer mortality as observed by the RERF group and formulated the LNT thesis for ICRP; but the doses received in low-dose-rate of the chronic radiation could produce only the beneficial immune effects to people and reduced their cancer death or mortality; as exceptionally experienced in the radiological incident in Taiwan. About 1700 apartments were contaminated by Cobalt-60, with about 10,000 residents lived in the apartments for 9 to 20 years and received quite large excess radiation dose average in about 0.34 Sv, high up to about 6 Sv unknowingly; But such large collective dose of radiation received by the residents did not increase their cancer mortality as predicated with the ICRP-60 1991 and the RERF investigation 1996 of the A-bomb survivors in Japan, On the contrary, the beneficial immune effects of such radiation received by the residents had reduced their spontaneous or natural cancer deaths to only about 3.4 % of the general population, as though the radiation has acted a vaccine in preventing cancers.. Such chronic radiation could also reduce the frequency of hereditary diseases. So that the radiation received in low-dose-rate or chronically (nomenclature hereafter as chronic radiation) from the Taiwan Co-60 contaminated apartments is always hormetic and could effectively immune of cancers as a vaccine. The radiation received instantaneously or acutely (nomenclature hereafter as acute radiation) as from the Japan nuclear explosion and the Chernobyl Nuclear Power Plant accident is quite different from the chronic radiation, even it has accumulated to high dose. The low-dose-rate of chronic radiation received in the Co-60 contamination in Taiwan is quite similar to the radiation received in the peaceful use of nuclear energy and medical use of man-made radiation, is also always hormetic and beneficial to humanity. Therefore chronic radiation should not be afraid but welcomed by public, and should be employed medically as immunity from cancers, and other diseases (Dr. Luckey even mentioned chronic radiation could reduce AIDS in animal experiment in his book “Radiation Hormesis). The conventional radiation protection policies, standards and measures for chronic and acute radiation should be conducted separately and differently. The theory of immune effects of chronic radiation could be also applied to other substances, such as toxic chemicals and microorganisms to humanity. High acute dose of arsenic, mercury and lead etc are harmful to humanity; but these elements in low ingredient are still used in some Chinese medicines today for improving health. The immune effects of chronic radiation experienced in Taiwan would give some new concepts to the radiation protection, and the medical immunity of cancers and other sickness, and there is of course non-linearity in biology, toxicology and medicine.

Key words: ^{60}Co-contaminated apartment; Chronic radiation; Radiation Hormesis; Cancer, mortality; Immunity from cancers and hereditary malfunction

HEALTH RISKS FROM FLUORIDATED WATER

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Eight years after the Curies discovered Polonium, other scientists found silicofluorides (SiFs) along with radiation in thermal waters of Aachen, Germany (Sahlbom N and Hinrichsen FW; "Titration der Kieselfluorwasserstoffsaure"; Berichte; 1906, pp 2609-2611). Exposure to "natural fluoride" and radioactivity in warm ground water is still being promoted as a benefit of Balneology. Today, 200,000 tons per year of commercial silicoflouride compounds (SiFs) are injected into US drinking water supplies serving over 150 million people to help suppress tooth decay. These SiFs are by-products collected when phosphate rock is converted to fertilizer and are likely to carry traces of radioactive uranium progeny. They have never been tested for health safety, a fact acknowledged to Congress by an EPA Assistant Administrator in 1999 and confirmed in 2000 in private communications with senior managers of EPA's Risk Management Research Laboratory. This situation is defended by EPA chemists on theoretical grounds supposedly proving that SiF treated water is "just like" water treated with sodium fluoride (NaF) at the level of 1 ppm of detectable F-. It is not; apart from latent radioactive contaminants, SiFs do not fully dissociate to leave behind only F- and silicic acid. Strong evidence exists for residues of incompletely dissociated SiFs that are powerful enzyme inhibitors. US health agencies (eg FDA, CDC, EPA, ATSDR, and NTP) and their contractors seem unaware of this. Animal tests designed to look for health effects of fluoridated water routinely use simple NaF as the fluoridating agent. Specific problems illustrating the seriousness of this disconnect are cited. For one, chronic SiF ingestion is strongly associated with elevated blood lead. In addition to the well-established CNS problems this may cause, however, there is good reason to suspect that a wide range of other low-level disorders can be attributed to chronic ingestion of SiF treated water.

SECONDARY ULTRAWEAK LUMINESCENCE FROM HUMIC ACIDS INDUCED BY GAMMA RADIATION

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Dried humic acid (HA) and its aqueous solution in 0.1 M were irradiated with 1-90 kGy doses of g-radiation. A secondary ultraweak radiation in the spectral range l=340-650 nm from irradiated solutions, but not from dry HA was recorded after the irradiation as a long-living chemiluminescence (CL). Absorption spectra (l=240-800 nm) of the irradiated solutions indicated on the polymerization/degradation of HA's macromolecules. The effect of and CL enhancers - luminol and lucigenin on the intensity and kinetics of CL proved participation of reactive oxygen species and the free radical mechanism in the CL and polymerization/degradation processes. The effect-dose functions (i.e. the intensity of the g-radiation-induced CL vs the dose of the g-radiation) have a non-linear shape, especially in the range of 1-10 kGy, suggesting complex radical mechanisms. A possible ecological significance of the observed phenomena is shortly discussed.

NON LINEAR DOSE RESPONSE RELATIONSHIPS IN THE DEFINITION OF OCCUPATIONAL EXPOSURE LIMITS

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Occupational exposure levels to chemicals are gradually going down thanks to improvements in technological requirements and regulations that increasingly designed to safeguard human health. Therefore the range of exposure levels, in some cases comparable to those in the general environment, can be considered as low level. Numerous international organisations, such as the Safety Health Administration (OSHA), the American Conference of Governmental Industrial Hygienists (ACGIH) and the Deutsche Forschungsgemeinshaft (DFG), have periodically issued and up-dated occupational exposure limits (OELs) for several chemical substances. The criteria on which these limits are based stem mainly from epidemiological studies. Although this methodology guarantees sufficient protection of exposed subjects, it does not usually take into account some specific characteristics of work environments, such as multiple exposure**,** combined exposure to physical and chemical agents and fluctuations in exposure levels In fact, in workplaces, multiple exposures to xenobiotics, that moreover vary over time in composition and effects, are not uncommon and the concurrent presence of physical factors could add uncertainty in health risk evaluation. Another factor to be taken into consideration is the inter-individual and intra-individual variability of exposed subjects, related to their specific physiological or pathological conditions. What seems however to be overlooked in the health risk evaluation process is the understanding of the effects of low level occupational exposure, that appears to be present even well below OELs. Lead is a case in point, since numerous studies show that it has effects well below the OELs indicated by numerous organisations. It would therefore seem necessary, after recital of a sincere "MEA CULPA", to take into consideration the real effects at low doses, which appear to be governed by biphasic dose-response relationships.

EFFECTS OF LOW-DOSE EXPOSURES TO X-RAYS ON THE NON-SPECIFIC ANTI-TUMOR RESPONSES IN MICE

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As shown by the results of our previous experiments, whole body irradiation of mice with a single low dose (0.1 and 0.2 Gy) of X-rays leads to the significant reduction of the number of tumor colonies induced in the lungs. This phenomenon can be related to stimulation of the activity of natural anti-tumour defence mechanisms.

In our experiments, BALB/c mice were irradiated with a single dose of 0.1, 0.2, or 1.0 Gy X-rays and then i.v. injected with L1 sarcoma cells. We detected that cytotoxic activity of natural killer (NK) cells obtained from spleens of the mice exposed to 0.1, 0.2, and 1.0 Gy was significantly higher than in the control, sham-irradiated counterparts. However, since the spleen cellularity was substantially reduced after irradiation with 1.0 but not with 0.1 or 0.2 Gy, and in view of the relatively low radiosensitivity of NK cells compared to B and T lymphocytes, it may be argued that the stimulatory effect of the former dose of X-rays was at least partially due to the NK-enrichment of the spleen cell populations obtained from mice exposed to 1.0 Gy. In addition, the interferon-γ (IFN-γ) stimulated peritoneal macrophages obtained from mice exposed to 0.1 or 0.2 Gy X-rays synthesized greater amounts of nitric oxide (NO) than macrophages collected from both the non-irradiated and 1.0 Gy-exposed mice.

The obtained data suggest that the inhibitory effect of single irradiations of mice with 0.1 and/or 0.2 Gy of X-rays on the development of pulmonary tumor colonies may result from stimulation of the natural anti-tumour defence reactions mediated by NK cells and/or cytotoxic macrophages.

EFFECT OF SINGLE WBI WITH LOW DOSES OF X-RAYS ON THE DEVELOPMENT OF AND BLOOD SUPPLY TO THE PULMONARY TUMOR COLONIES IN MICE

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The purpose of the present study was to investigate the effect of whole body irradiation (WBI) of mice on the development of and blood supply to the induced neoplastic colonies in the lungs. BALB/c mice were irradiated with a single dose (0.1; 0.2 or 1.0 Gy) of X-rays and then i.v. injected with L1 sarcoma cells. The superficial tumor colonies in the lungs were counted 14 days later. In histological slides obtained from the colonies blood supply was calculated as the total area of erythrocytes' profiles related to the total area of the tumorous tissue. In addition, expression of the beta3 subunit of the alphavbeta3 integrin was estimated on the surface of the B16 melanoma cells pre-exposed to 0.1 or 1.0 Gy of X-rays.

The results indicate that the number of tumor colonies was lower in animals pre-exposed to 0.1 or 0.2 Gy than in those irradiated with 1.0 Gy (58.6%, 64.8 and 89,9%, respectively, of the control value calculated for the sham-exposed mice). Concurrently, the total area of the erythrocytes profiles in the vessels of the growing tumors was significantly reduced in mice exposed to 0.1 Gy compared to the sham-irradiated animals or to those exposed to 1.0 Gy (7%; 14% and 23% of the total area of the tumorous tissue, respectively). Interestingly, as revealed by the fluorimetric analysis, exposure of the B16 cells in suspension to 0.1 Gy but not to 1.0 Gy X-rays led to the significant decrease in the expression of the beta3 integrin subunit on these cells (79% vs. 119%, respectively, of the control value obtained in the sham-irradiated cells).

These results suggest that the inhibitory effect of 0.1 Gy X-rays on the growth of pulmonary tumor nodules may be causatively related to inhibition of the development of blood vasculature in the nodules.

HETEROGENEOUS EXPOSURE DOSE LEVELS UNABLE TO INDUCE HARMFUL EFFECTS OF LIFE EXPECTANCY AND BLASTOMOGENESIS

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The goal of present report consists in the result analysis for many years of experiments to evaluate dose levels for incorporated radionuclides which do not induce blastomogenic effects and do increase the average life expectancy in experimental animals. Experimental data on more than 5,000 white rats (without strain selection) are generalized. The comparison of literature data on cancer incidence in human exposed to radiation has given the opportunity to conclude that direct extrapolation of experimental data on human is possible. It was found that experimental and epidemiology data indicate to dose level unable to induce critical organ tumors for incorporated alpha emitters (^{252}Cf, ^{241}Am, ^{239}Pu, ^{237}Np etc) is 0.2-1.4 Gy (skeleton), 0.4-0.8 Gy (lungs);for beta emitters (^{144}Ce, ^{90}Sr) these dose levels are 12-14 Gy (skeleton). In case of the exposure to ^{131}I the dose unable to induce thyroid tumors is < 0.3 Gy; for ^{90}Sr and ^{137}Cs the dose unable to induce leukemias is < 0.2-0.5 Gy. Analysis of dose-effect relationships as related to average life span of rats gives evidence for hormetic effects in a dose range up to 10-12 Sv in critical organs, following incorporation of radionuclides having different biokinetic parameters and types of radiation, and administered by various ways. The obtained actual research data on the health effects of low doses of ionizing radiation contradict to hypothetical linear non-threshold dose-effect ratio.

STRESS RESPONSE AND CELLULAR LONGEVITY: THE PROLONGED LIFESPAN OF CUSHING'S-SYNDROME-PATIENTS' FIBROBLASTS

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Glucocorticoid (GC) hypersecretion constitutes the major hormonal response to stress. Patients suffering from Cushing's syndrome are characterized by chronic endogenous GC excess, and thus by severe alterations in tissue homeostasis, such as dermal atrophy and impaired wound repair. In the present study we have investigated features of skin fibroblasts derived from Cushing's syndrome patients when grown *in vitro*, in order to gain insight into the impact of a long-lasting exposure to high GC levels *in vivo* on the cellular physiology. Accordingly, we have developed primary fibroblast cultures from Cushing's syndrome patients and sex- and age-matched normal donors, and we have studied: a) crucial parameters of tissue homeostasis, such as their proliferative capacity, secretion of collagen, matrix metalloproteases, and tissue inhibitors of metalloproteases, as well as, the cells' capacity to contract collagen lattices, and b) the lifespan of these cells and aspects related to cellular longevity, such as transforming growth factor-beta (TGF-beta) secretion and heat-shock protein-70 (HSP70) induction by stress. Cushing's syndrome patients' fibroblasts (CF) exhibit higher proliferation rates, compared to normal donors' fibroblasts (NF). They are characterized by increased collagen accumulation and collagen-lattice contraction compared to NF. Interestingly, CF's lifespan, when cultured *in vitro* under standard conditions, is significantly prolonged compared to NF. This extension could be possibly explained by the fact that CF, in comparison to NF, secrete lower levels of TGF-beta — known to be implicated in stress-induced premature senescence — and also exhibit much more intense stress reaction, in terms of HSP70 induction. In conclusion, Cushing's syndrome patients' skin fibroblasts, after their transfer to *in vitro* culture exhibit a "rebound" reaction, leading to an "anabolic" phenotype, as well as to ameliorated stress response and prolonged life-span. These results support the hypothesis that stress response may have beneficial consequences in cellular longevity, as well as in tissue homeostasis.

HORMETIC EFFECTS AT CLINICAL LEVELS

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Introduction

The concept of hormesis has been gaining increasing scientific support over the past few years. Basic ideas such as the ability of repeated mild stimulation to bolster defences against biological ageing have been validated in several laboratory experiments. Although hormetic influences are clearly encountered at the cellular and molecular level, little is known about the effects of hormesis at an organismic level. It is, however, possible to suggest that hormesis has influences which transcend basic biological boundaries and can also be encountered at higher levels. Mild repeated stimulation or appropriately time 'challenges' may be used at the clinical level in order to attempt to influence the impact of age-related disease and dysfunction.

Methods and Results

Examples of stimulation or challenges which exhibit hormetic effects include dietary restriction (the only intervention which has repeatedly been shown to increase lifespan), physical and mental exercise, end even social and spiritual stimulation. Dietary restriction can be interpreted as a nutritional challenge which places the organism under nutritional stress, stimulating several biochemical repair pathways. Physical exercise, if appropriately timed and sufficiently varied, can induce hormetic effects at the level of the muscles, arteries, heart and lungs. Mental challenges such as brain and memory training, sense exercises and positive ageing thinking, are all aimed at increasing the complexity and integration of interacting neural stimuli, resulting in a reduced likelihood of age-related brain dysfunction. Social and spiritual stimulation aimed at reversing age-related loss of dynamical complexity, act upon even higher levels to ensure a reduction of social isolation and other social problems.

Conclusion

It is suggested that hormetic effects can be shown not only at basic biological levels but also at higher levels, and that the integration of these hormetic effects may help reduce the likelihood of age-related disease in a clinical setting.

SYNERGY – THE EFFECT OF COMBINING NON-LINEAR DOSE PROFILES: THE PREDICTION AND QUANTIFICATION OF THE POTENTIATION OF EDTA WITH ANTIMICROBIALS

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Background: EDTA is potentiator of many antimicrobials including antibiotics, reducing the MIC of specific antimicrobials against *Pseudomonas aeruginosa* by a factor of up to 100. This study examined the hypotheses that the potentiation could be mathematically modeled and that this model could be used to predict the effect of combining EDTA with any antimicrobial against *Ps. aeruginosa*.

Methods: The inhibition profiles of EDTA, several antimicrobials (antibiotics and antimicrobial biocides) against a range of organisms were obtained. A checkerboard-type methodology was used to examine EDTA/antimicrobial combinations. The data obtained from turbidometry were analysed using a non-linear additive equation developed for the examination of antimicrobial mixtures.

Results: EDTA shows a biphasic inhibition profile (a plot of inhibitor concentration against growth) against *Ps. aeruginosa* but not with *Staphylococcus aureus*. Mixtures of EDTA with quaternary ammonium surfactant biocides or with clinical antibiotics exhibited potentiation against *Ps. aeruginosa*, but not with *St. aureus*.
The potentiation effect of EDTA/ antimicrobial mixtures on *Ps. aeruginosa* was successfully modeled as two linked events. 1. At low EDTA concentrations (EDTA<800mg/l), an additive effect of antimicrobial/EDTA mixtures is observed. 2. At high EDTA concentrations (EDTA>800mg/l), removal of, or damage to the outer membrane, presents an organism more easily inhibited by the adjunct antimicrobial, and its apparent MIC is reduced, e.g., the MIC of ampicillin is reduced from 1260mg/l to 20 mg/l by EDTA in excess of 800 mg/l.
The modeled parameters found were used to predict the potentiation of other antimicrobials, the predictions were verified by experiment.

Conclusions: The potentiation effect of EDTA on antimicrobials against *Ps. aeruginosa* can be wholly predicted and quantified. This may have therapeutic implications e.g. for prophylaxis in Cystic fibrosis treatments.

EFFECT OF LOW AND VERY LOW DOSES OF SIMPLE PHENOLICS ON PLANT PEROXIDASE ACTIVITY

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Peroxidases, very important hemoprotein oxidoreductases, are common in all types of living organisms and catalyze the process of aromatic substrate oxidation at the expense of H_2O_2. These enzymes are crucial for polyphenol biosynthesis in plants and fungi owing to oxidation and the recombination of phenolic free radicals. In the previous announcement (Malarczyk *et al.*, 2002, Materials of Non-linear Conference, BELLE, Amherst, MA, USA) we showed that the activity of pure horseradish peroxidase (Sigma) was distinctly modified in the presence of low doses of guaiacol ranging from 100^{-1} to 100^{-20} (mol/L). The amplitude between maximal and minimal activity reached about 1000 nkatals. In the presented experiments we analyzed how the same enzyme behaved in the presence of low doses of simple phenolic substances which vary in the type of functional groups at the aromatic ring. These were –OH, -COOH, -CHO, $-CH_3$ in various configurations common in natural phenols, methoxyphenols, phenolic acids and aldehydes. The highest amplitude of about 2000 nkatals was observed for phenol, vanillic and isovanillic acids and their aldehydes. In the second group, catechol and pirogallol were found. The smallest amplitude characterized substances rich in $–OCH_3$ such as veratrol, anisol, and their derivatives. All these results were analyzed by polynomial regressing analysis. The obtained curves ceased to oscillate in the case of methoxylic compounds such as veratrol and anisol, when the rate of dissolution increased. On the other hand, in the case of phenolic substances such as phenol, catechol, vanillic and isovanillic compounds, the amplitudes of polynomial curves had the same oscillating character from the beginning to the end of the experiments. These observations come us to the conclusion that mainly –OH groups and also the relation between the numbers of –OH and $–OCH_3$ groups at the aromatic ring are very important for the stabilization of described effect of phenolic substances on the peroxidase molecule during their catalytic activity. The protection of the active center of this enzyme by hydroxyl groups of phenolic compounds is very probable.

THE USE OF STREPTOLYSIN O FOR THE TREATMENT OF SCARS, ADHESIONS AND FIBROSIS

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Diseases and conditions involving the formation of excessive amounts of collagen and other connective tissue include scleroderma, fibrosis, and scar and surgical adhesion formation. This may result from acute and chronic inflammation, disturbances in the normal parenchymal area, and activation of fibroblasts. One possible treatment for such collagen-related disorders is ML-05, a modified form of the hemolytic and cytotoxic bacterial toxin, streptolysin O (SLO). At sublytic concentrations *in vitro*, ML-05 was shown to activate CD44 expression. This may modulate production of collagen, hyaluronate and their associated enzymes to allow a restoration of normal extracellular matrices within tissues. More importantly, ML-05 appeared to alter skin collagen mobilization in two *in vivo* models of collagen disorders, the tight skin mouse (TSK) model for scleroderma, and the bleomycin-induced mouse skin fibrosis model. In the TSK model, a 25% decrease in hydroxyproline (a measure of total collagen) in the TSK+SLO group relative to the TSK+saline group was observed at 6 through 8 months. In the bleomycin-induced skin fibrosis study, a reduction in hydroxyproline levels in one treatment group ranged from 15-22% over a six-week period (relative to levels in a bleomycin-induced, untreated control group). Hydroxyproline levels in samples from this treatment group were only slightly greater than levels in an uninduced control group at 8 weeks. Thus, SLO treatment appeared to mobilize or reduce collagen levels in two separate mouse skin fibrosis models, one genetically based and the other chemically induced. Further evaluations of ML-05 activity in modulating collagen formation are in progress.

THE USE OF LOW DOSE THIMEROSAL FOR THE TREATMENT OF HERPESVIRUS INFECTIONS

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In 1974 Dr. J.R. Miller reported the successful treatment of oral herpes lesions by the subcutaneous injection of a sub-vaccine dose of influenza virus. He hypothesized that the influenza virus somehow neutralized the herpes agent by interfering with its replicative cycle and simultaneously inducing a localized analgesia that brought relief to the lesion site within minutes.

We repeated Miller's observations and then isolated the active component of the influenza vaccine, finding it to be the vaccine preservative thimerosal. Subsequently we documented *in vitro* and *in vivo* anti-herpes activity at a concentration of thimerosal significantly below that used for preservative purposes.

COMPARISON *IN VIVO* STUDY OF GENOTOXIC ACTION OF HIGH VERSUS VERY LOW DOSE-RATE γ-IRRADIATION

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The aim of the present study was to compare genotoxicity induced by acute versus chronic exposure of mice to γ-radiation within a dose range of 5 to 60 cGy using the single cell gel electrophoresis (comet) assay and the micronucleus test. CBA/lac male mice were used in the study. Animals were irradiated at a dose rate of 47 cGy/min (28.2 Gy/h, high dose-rate) or 60 cGy/year (~0.07 mGy/h, very low dose-rate). Both dose-rates were generated by Cs^{137} sources of γ-radiation. The comet assay study on spleen lymphocytes showed that very low dose-rate irradiation resulted in statistically significant increase in nucleoid relaxation (DNA breaks), starting from a dose of 20 cGy. Further prolongation of exposure time and, hence, increase of a total dose did not, however, lead to further increase in the extent of nucleoid relaxation. Thus, the levels of nucleoid relaxation of mouse spleen lymphocytes after 20 cGy or 60 cGy doses of low dose-rate γ-irradiation were about the same and corresponded to a level of nucleoid relaxation induced by a dose of 10 cGy of high dose-rate exposure. It is noteworthy that the increase in spleen lymphocytes nucleoid relaxation induced by low dose-rate γ-irradiation is accompanied by decrease in their sensitivity to hydrogen peroxide as measured by the comet assay as well. Most likely, the low-level exposure-induced increase in nucleoid relaxation is caused by structural changes of chromatin and/or activation of proliferation of the spleen lymphocytes, rather than direct formation of DNA lesions by irradiation. The bone marrow micronucleus test revealed that increase in polychromatic erythrocytes with micronuclei over a background level was induced by very low-level γ-irradiation with a dose of 60 cGy only, with the extent of the cytogenetic effect being similar to that of 10 cGy high dose-rate exposure. These results indicate good correlation between the two assays applied in our investigation although nucleoid relaxation does not necessarily lead to cytogenetic damage and different cell types were assayed. Taken together, our data suggest that mutagenic potential of chronic γ-irradiation with a dose-rate of 60 cGy/year is about 6-times lower than that of high dose-rate γ-irradiation. Thus, presented results support the hypothesis of non-linear treshold nature of biological action of chronic low dose-rate irradiation.

EFFECT OF LOW DOSE OF CADMIUM ON TRANSFORMATION OF NORMAL HUMAN PROSTATE CELLS

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Cadmium is an environmental pollutant with many harmful effects and is linked to several human cancers such as lung, nasal sinuses and prostate. However, exposure to low doses of toxic agents has been reported to have stimulatory effects in a number of models, a phenomenon known as "hormesis". Biologically advantageous effects of low-level exposure to cadmium were demonstrated in different studies. In a study with mouse cells hormetic activity from low doses of cadmium chloride was correlated with increased levels of Hsp 70 and metallothionein (MT) indicating a stress response. In the present study we have evaluated the protective effects of low dose cadmium treatments in normal human prostate cells. RWPE-1, normal prostate cells, were exposed to low doses (10^{-6}, 10^{-7}, 10^{-18}, 10^{-21}, 10^{-32} and 10^{-36} M) of cadmium for 20 weeks followed by a treatment with 10^{-5} M cadmium for another 8 weeks. Growing these pretreated cells further in normal media for 3-4 weeks resulted in transformation. However, the cells pretreated with low doses of cadmium were significantly slower in developing the transformed cell mounds compared to controls. In addition, the number of transformed cell mounds was lower in pretreated cells indicating protective effect of low dose pretreatments.

HORMETIC MODULATION OF AGING AND LONGEVITY IN FRUITFLIES

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One of the major concepts emerging from research in biogerontology is that of aging as a failure of maintenance. The ability of living systems to respond to internal and external sources of damage, such as free radicals, ultraviolet radiation, heavy metals, toxins and thermal stress, is an indicator of their property of homeostasis. Therefore, one approach is to use repeated challenge as a stimulator of maintenance and repair pathways resulting in the modulation of the aging process. Of various experimental systems used in aging and longevity research, the use of insects, especially the fruitflies, has proved to be very useful. Their short lifespan, convenience of laboratory maintenance and a large body of biological and genetic information make them an attractive experimental system for biogerontological research and modulation. Some of the stresses which have been used by us and others to slow down aging and to prolong the longevity of fruitflies include pro-oxidants, irradiation, ethanol, ultraviolet irradiation, heat shock, starvation and hypergravity. Further studies are required to fully understand the molecular mechanisms of distinction between mild and severe stress, and how single or repeated exposure to stress bring about a whole range of physiological improvements, including a delay in the onset of various aging characteristics and prolongation of lifespan.

ALCOHOL AND BLOOD PRESSURE: A COMPLEX NONLINEAR RELATIONSHIP

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Epidemiologic studies in the past several decades have firmly established a relationship between regular, heavier alcohol consumption and increased blood pressure (BP) or hypertension (HTN). This association has been demonstrated in both cross-sectional and prospective studies in both sexes and various ethnic groups. It is independent of usual type of alcoholic beverage, adiposity, education, smoking, salt intake, and several other traits. Using any BP cut-point as definition, HTN prevalence is approximately doubled among heavy drinkers. Clinical experiments have demonstrated a subacute effect; i.e., among drinkers of 3-4 standard drinks per day BP falls in days to weeks with abstinence from alcohol and similarly rises again after resumption of drinking. Studies of the role of alcohol in HTN sequelae, such as coronary heart disease and stroke, have been difficult because of the effects of alcohol, independent of BP, in these conditions. Overall, it is likely that this alcohol-HTN relationship is causal. Most of the studies show a threshold alcohol-HTN relationship, with no BP relationship at lighter (<3 standard drinks per day) and a progressive BP increase at $\geq$3 drinks daily. Several studies, including the Kaiser Permanente and Nurses' Health Studies, have shown slightly lower BP's among lighter alcohol drinkers than among abstainers.
This J-shaped alcohol-BP curve has been seen more often in women than in men, and might be due to confounding by healthier life-style habits of female light drinkers. At the upper end of the drinking spectrum, very heavy drinkers (those reporting $\geq$9 drinks/day in Kaiser Permanente data) show lower BP's than less heavy drinkers; i.e., a downturn in the alcohol-BP curve. Speculatively, this has been attributed to major debilitating alcohol-related illnesses (e.g., liver cirrhosis, cardiomyopathy) among very heavy alcohol users. The alcohol-BP relationship is clearly non-linear; the unexplained paradoxes are of scientific interest and have practical clinical implications.

PARTICULATE MATTER (PM) INCREMENTS MAY NOT BE CAUSAL IN MORTALITY AND MORBIDITY

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Numerous statistical analyses find positive correlations between increments in ambient PM levels and increments in disease and death rates. These associations persist to PM levels below air quality standards, and are at odds with the toxicology of PM chemical constituents. The unusual level of lethality per unit PM mass predicted by epidemiologic associations may instead be due to confounding by unmeasured societal, behavioral, or stress factors. PM levels logically correlate with societal "stress and activity level," because increased societal activity causes increased PM emissions. Also, people's sense of health and actual health depend on societal and psychological factors. For example, a stress such as anger is found to be strongly associated with increased risk of death due to heart attack. Studies also show important effects of stress on the symptoms and severity of asthma. The ability of societal "stress and activity level" to cause fluctuations in mortality and morbidity is demonstrated by calendar-related changes in mortality that appear unrelated to chemical exposures. For example, upward swings in cardiovascular and respiratory mortality have been demonstrated to be correlated to the day of the week, to the first day of the month, the fourth day of the week, and to the first week of the year. These "calendar risks" are not based on toxicologic exposures. In order to rule out the possible role of such non-toxicologic variables in the PM associations, quantitative surrogates for societal stress (*e.g.*, daily sales, auto traffic, electricity usage, noise levels, telephone traffic) must be tested as alternatives to the PM variable in the statistical models. Without a vigorous effort to challenge the role of the PM variable, it would be erroneous to conclude that every decrement in PM leads to an improvement in health.

EPIDEMIOLOGICAL EVALUATION OF THE THRESHOLD MODEL FOR HEXAVALENT CHROMIUM

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The primary target for hexavalent chromium (Cr(VI)) carcinogenicity is the respiratory tract. Though hexavalent chromium readily transits cell membranes, several airway defense mechanisms exist, resulting in reduction to Cr(III) and/or elimination of Cr(VI) particles before reaching alveoli. The human body's capacity to reduce and detoxify hexavalent chromium suggests a threshold mechanism. Indeed, some have suggested that Cr(VI) is carcinogenic only when the dose overwhelms the body's reduction capacity. We evaluated the evidence for a threshold effect in two epidemiological studies of chromate production workers. One study included 492 workers employed at a Painesville, Ohio, chromate production plant between 1940 and 1972 (Luippold et al., in press). The second study comprised 2,357 workers employed at a Baltimore, MD, chromate production facility between 1950 and 1974 (Gibb et al., 2000). The vital status of workers in these cohorts was determined through 1997 and 1992, respectively. Standard Mortality Ratios (SMRs) for lung cancer in relation to cumulative Cr(VI) exposure were computed using local mortality rates, adjusting for gender, race, and calendar year. Both studies employed a 5-year lag, enabling us to pool the data to evaluate the exposure-response relationship over a wide range of exposure levels. SMRs steadily increased from 96 (95 percent confidence interval (CI) = 63-138), 142 (CI = 95-201), 224 (CI = 160-303), 240 (CI=137-390) to 519 (CI = 259-928) for an average cumulative exposure of 0.00045, 0.0042, 0.45, 0.89 and 6.99 mg/m^3-years, respectively. A linear regression model using the iteratively re-weighted least squares method fit the pooled data reasonably well ($X^2 = 8.22$, p=0.22). The linear model fit the Painesville data better ($X^2 = 1.11$, p=0.57) than the Baltimore data ($X^2 = 3.41$, p=0.18). Data from the two most informative epidemiological studies, considered either separately or combined, do not support the threshold hypothesis for the lung carcinogenicity of Cr(VI).

THE APP PROMOTER RESPONDS TO PB EXPOSURE IN TRANSFECTED PC12 CELLS

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The predominantly sporadic nature of Alzheimer's disease (AD) and the occurrence of neurodegenerative processe in the aging brain suggest that the environment may play a role in the development of AD. AD is characterized by excessive deposits of aggregated beta-amyloid peptides (*Aβ*), which are snippets of a larger protein, the *β*-amyloid precursor protein (APP). Therefore, any agent, which results in the overproduction of APP, would also elevate the formation of A*β*, eventually leading to the neuropathological changes of AD. The regulatory region of the APP gene contains elements recognized by the transcription factor Sp1, which is essential for the activation of the APP gene. Exposure to lead (Pb) has been previously shown by us to induce Sp1 activity. To test the hypothesis that Pb may induce APP gene expression, we transfected PC12 cells with the human APP promoter linked to a reporter gene (luciferase). The responsiveness of the promoter was tested over time in the presence of nerve growth factor (NGF) and low levels of Pb. We found that the presence of Pb stimulated APP promoter activity in a time and dose-dependent manner suggesting that Pb exposure may be a potential risk factor for the promotion of amyloidgenesis.

LOW DOSES GAMMA-RADIATION INDUCE NON-LINEAR DOSE RESPONSE IN MAMMALIAN AND PLANT CELLS

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The induction of cytogenetic damage (per cent of cells with chromosome aberrations or micronuclei) by low doses of acute (dose rate 47cGy/min) and chronic (dose rate 0.01cGy/min) gamma-radiation was studied on the culture of Chinese hamster fibroblasts, human lymphocytes, *Vicia faba* seeds and seedlings. The sensitivity of these objects to low range were greater than it was calculated by extrapolation from higher to lower doses. The obtained dose-response curves of cytogenetic damage are described by step function. At very low doses the curves can be fitted by a linear regression, then turn a plateau and at last the curves became linear again, but with another slope angle. There is no statistically significant difference between the yields of cells with micronuclei induced by low doses of chronic and acute radiation in the examined dose range. Similar data were obtained both for human lymphocyte culture and for roots and seeds of *Vicia faba.* In our experiments it was revealed that dose range in which the plateau occurs varied with biological objects. We have shown that the modifying effect of repair inhibitor caffeine and radioprotector mercaptoethylenamine (MEA) is absent at low doses of gamma-radiation and caffeine did increase the number of cells with cytogenetic damage in the dose interval of the plateau. In the presence of MEA, the plateau extends up to 2Gy. This is evidence that the plateau does exist. Our results suggest that the initiation of repair occurs only at a definite level of damage and that the increased yield of cytogenetic damage at low radiation doses is attributable to an insignificant contribution or the absence of repair processes.

EFFECT OF MIXED RARE EARTH CHANGLE CROSSING PLACENTA MEMBRANE ON EMBRYO CELL DNA DAMAGE

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To assess the potential health risks of mixed rare earths Changle for human embryo whether it crosses placenta membrane, or placenta barrier should be determined firstly. The morphology of placenta was observed in light and electron microscope to realize distribution and destiny of mixed rare earth changle in placenta tissue, meanwhile the level of mixed rare earths changle in serum of pregnant rat, amniotic fluid and extract of embryo tissue were measured by using Inductively Coupled Plasma-Mass Spectrometer (ICP-MS). Secondly to detect DNA damage of embryo cell we chose micronucleus test and single cell gel electrophoresis (SCGE). The rats were administered respectively $0.3mg{\cdot}kg^{-1}$, $2mg{\cdot}kg^{-1}$, $5mg{\cdot}kg^{-1}$ and $20mg{\cdot}kg^{-1}$ mixed rare earths Changle every day by oral from 6th to 18th day after pregnancy. The results showed that many particles were found in syncytialtrophoblast of placental villi under light microscope, they are the dense bodies with envelope under electron microscope in contaminated groups. Results of ICP-MS assay indicated that the level of Ce increased with contamination dose in the serum of pregnant rats, the level of total rare earth element remarkably rose in amniotic fluid and serum of pregnant rats for $20mg{\cdot}kg^{-1}$ group. Also the amount of cells with micronucleus and comet star cell significantly increased with increasing contamination dose, which appeared to be a dose-effect relationship. In conclusion, the placenta barrier has limitary effect on mixed rare earths changle, but it still can enter fetus body when it accumulates enough and caused DNA damage of the hepatocyte and developing erythrocyte of rat embryo.