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BELLE: AN EVOLVING LEGACY

A brief history of BELLE: Introduction

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ABSTRACT

This paper introduces an issue of the BELLE Newsletter that is designed to reflect on the role of BELLE in affecting how the concept of hormesis is perceived and accepted by the biomedical and toxicological communities. A brief overview of how BELLE was created is provided.

Key Words: *hormesis, hormetic, biphasic, dose response, U-shaped, J-shaped, adaptive response*

INTRODUCTION

In 1985 the Electric Power Research Institute (EPRI) organized the first conference on the topic of hormesis under the leadership of the late Dr. Leonard Sagan. I remember receiving a preliminary conference brochure during the early part of 1985 which described this conference on radiation hormesis. Upon reading the brochure it reminded me of my earlier research on the effects of plant growth inhibitors. I had observed that the application of such inhibitors stimulated the growth of several plant species when applied at low concentrations but were inhibitory at higher concentrations. I researched this question for about three years

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through my undergraduate and Master's Degrees before deciding to switch fields to become a vertebrate toxicologist. While I did not know it at the time, what I had observed were cases of hormesis, a low dose stimulation and a high dose inhibition. When our work was published (Calabrese and Howe 1976) we simply used the terms low dose stimulation/high dose inhibition, as the term hormesis was not known to us. However, when I read the EPRI brochure, I saw a conceptual connection between the biphasic dose response described in their brochure and my more than a decade old research on plants. This motivated me to call Dr. Sagan and to discuss my plant research history with biphasic dose responses. This conversation led to an invitation to attend the meeting and to present a paper on chemical hormesis, even though the conference was entitled radiation hormesis. This conference was held in Oakland, California in August of 1985, with a peer-reviewed conference proceedings being published two years later in the journal Health Physics. In 1989 Dr. Sagan and Professor Sheldon Wolff, University of California at San Francisco, participated in a point-counterpoint debate in the journal Science on the topic of hormesis (Sagan 1989; Wolff 1989). The reading of their debate inspired a second telephone call to Dr. Sagan. The gist of the conversation was that the concept of hormesis may be important to the biomedical and risk assessment communities but that the science underlying it was unresolved. Until it was resolved or significantly better understood, it would have little impact on society. We pledged that we would work to ensure that over the next decade significant scientific activities would be directed to this issue.

THE FORMATION OF BELLE

As a result of this conversation, Dr. Sagan and I held a meeting of about 15 toxicologists from government, industry and academia, in May 1990, at the University of Massachusetts at Amherst in order to discuss the topic of hormesis and how we could organize to enhance research interest on the topic. It was at that meeting that the BELLE organization was formed with the acronym BELLE being created by Dr. Donald Hughes, then working at the Proctor and Gamble Company in Cincinnati. One of the early projects of the BELLE organization was the creation of a newsletter (called the BELLE Newsletter), which was to be a scholarly publication that would help to direct and stimulate scientific focus and debate on the issue of low dose effects in general, with particular focus on hormesis. In addition, BELLE directed a series of workshops and conferences, always publishing the results of these activities in either monographs of journals (e.g. Environmental Health Perspectives, Journal of Applied Toxicology). These activities proved important as they offered a vehicle to researchers in the biomedical and toxicological communities to discuss hormesis and related topics, the opportunity to identify other researchers interested in biphasic dose responses, to compare molecular mechanisms underlying the hormetic phenomenon and to discuss the clinical or risk assessment implications of their findings. Within several years, the BELLE Newsletter became well known within the toxicological community and co-published within the journal Human and Experimental Toxicology. The progressive interest in hormesis became increasingly evident as seen by citations within Pub Med and the Web of Science. By the early 2000s the hormesis concept had been integrated into all leading textbooks on toxicology, incorporated into numerous university courses on toxicology, and became a mainstream concept within the biomedical sciences and toxicology (Hoffmann 2009; Scott 2008, 2007; Calabrese and Baldwin 2004, 2003, 2001; Calabrese et al. 1999). This successful progression of hormesis concept penetration within a scientific community that was unaccepting of hormesis up through the 1980s (Calabrese 2009a,b, 2005) was as unexpected as it has been rewarding. While it has taken the efforts of many to achieve this growth, it equally demonstrates the intellectual openness of the scientific community to new and challenging ideas. This issue of the BELLE Newsletter is one in which members of the BELLE Advisory Committee were invited to offer their reflective comments on what BELLE has achieved science its creation, especially with respect to taking the concept of hormesis from its highly marginalized status to one of centrality within the field.

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HORMESIS IS CENTRAL TO TOXICOLOGY, PHARMACOLOGY AND RISK ASSESSMENT

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ABSTRACT

This paper summarizes numerous conceptual and experimental advances over the past two decades in the study of hormesis. Hormesis is now generally accepted as a real and reproducible biological phenomenon, being highly generalized and independent of biological model, endpoint measured and chemical class/physical stressor. The quantitative features of the hormetic dose response are generally highly consistent, regardless of the model and mechanism and represents a quantitative index of biological plasticity at multiple levels of biological organization. The hormetic dose response model has been demonstrated to make far more accurate predictions of responses in low dose zones than either the threshold or linear at low dose models. Numerous therapeutic agents widely used by humans are based on the hormetic dose response and its low dose stimulatory characteristics. It is expected that as low dose responses come to dominate toxicological research that risk assessment practices will incorporate hormetic concepts in the standard setting process.

Key Words: hormesis, hormetic, biphasic, U-shaped, adaptive response, inverted U-shaped

INTRODUCTION

This paper discusses insights that have been gained as a result of assessing the concept of hormesis since approximately 1990. Of the two dozen new findings and ideas that will be discussed in this paper essentially all were unexpected. Of particular surprise was that prolonged and detailed assessment of the nature of the dose response, especially in the low dose zone, would provide important and basic conceptual insights that have relevance to all biological systems. Thus, while the plan was to assess hormesis, the journey has yielded far more than was anticipated. Each discovery/insight is briefly described and referenced. It is hoped that the reader will be intrigued by the range of biological insights that studying the hormesis concept has revealed. Furthermore, this paper will provide a useful and concise summary of the current status of hormesis related research as well as insights into possible future developments.

CRITICAL FAILURE OF PUBLIC HEALTH REGULATORY AGENCIES TO VALIDATE THE THRESHOLD DOSE RESPONSE MODEL IN THE 20TH CENTURY

The threshold dose response model is fundamental to all aspects of biology that use dose response relationships. This model has been central to toxicology, pharmacology and public health regulatory agencies since the 1930s, affecting chemical/drug safety evaluations, modern risk assessment practices and public health exposure standards. The study and application of the threshold dose response model is therefore central to the fields of toxicology, pharmacology and risk assessment (Calabrese 2009a,b; Calabrese 2008o).

This centrality of the threshold dose response model within the biomedical sciences and public health regulatory agencies has lead to the assumption that this dose response model has been studied in detail, scientifically vetted and validated, and can be reliably assumed to provide accurate estimates of biological responses especially in the low dose zone (i.e. below toxicological and pharmacological thresholds). In the course of our assessment of hormetic dose response relationships, the question was raised as to whether the threshold dose response was formally assessed for its capacity to predict below threshold responses. While there was the general belief that it must have been, given the importance of this question and the universal acceptance of this model within the scientific and regulatory communities, our comprehensive attempts to find research that had addressed this issue uniformly failed. Yet this failure was very unsettling, for how could the biomedical community have built an entire toxicological and drug testing and regulatory framework upon a dose response model that had not been validated? This seemed to be implausible and therefore could not possibly be true. It most likely meant that our comprehensive attempts were not really "comprehensive" and that we must have been missing the obvious. Yet renewed attempts with differing search strategies to ferret out the scientific vetting of the threshold dose response model continued to fail to yield any relevant publications. Eventually a disturbing conclusion was reached, that is, the principal dose response model upon which chemical and drug toxicity testing has been based had never been validated, but simply accepted as true, being passed down with authoritative conclusionary state-

ments from textbook to textbook, from professor to student, from regulatory agencies to citizens, across generations of scientists, creating an illusion of knowledge and informed guidance.

This situation led to two avenues of further inquiry. The first was the need to develop an historical reconstruction of the threshold dose response concept that would have lead to how this "blind" acceptance without validation and vetting occurred (see Calabrese, 2005a for a detailed assessment). The second critical issue was the need to test predictions of the threshold dose response model in large data sets using a priori entry and evaluative criteria (Calabrese and Baldwin, 2001, 2003a, Calabrese et al., 2006a,b; 2008). That is, we would conduct our own vetting of the threshold dose response model to make accurate predictions of responses below the threshold. These studies have documented that the threshold dose response very poorly predicts responses below the estimated threshold, a performance that was broadly generalizable. This failure of the threshold model to make accurate predictions of responses below the threshold in the above published data was also consistent with the publication of a large number of studies within the hormesis database (Calabrese and Blain, 2005; 2009) that are supportive of the hormesis dose response and not the threshold model.

These findings point to a critical and ongoing failure of the scientific and regulatory communities to properly validate models, especially ones that are directly used to affect public health and medical practices. The societal costs of the failure to vet and validate the threshold dose response model for the past 75 years are unknown. However, one must ask how it was possible for U.S. federal agencies such as the EPA, FDA, ATSDR, NIEHS, NIOSH, OSHA and others to never conduct or fund studies that would have addressed this question. The same question may be asked of private sector funding of toxicological and pharmaceutical research and why this question has never been addressed.

It should be noted that the FDA did recognize the need to validate linearity at low dose predictions in the mid 1970s, with the megamouse testing of the carcinogen 2-AAF. However, this effort revealed that risks lower than 1/100 were not practically achievable for carcinogens within chronic animal bioassays. The failure of the study to adequately test linearity at low dose modeling, despite the use of enormous resources (e.g. 24,000 animals), lead to a continued reliance on non-validated models for risk assessment of chemical carcinogens. An important irony was that a detailed analysis of the FDA/2-AAF study by an expert panel of the US Society of Toxicology revealed an unequivocal hormetic dose response for bladder cancer with risks decreasing below the control group at low doses (Bruce et al., 1981).

HORMESIS: IT IS REAL AND COMMON

When the BELLE Advisory Committee was first organizing there was no generally accepted position on what was the status of hormesis within the scientific community. However, there were considerable questions over whether it was a real, reproducible phenomenon. Its status within the scientific community in the late 1980s and early 1990s was marginal at best. In fact, from 1945-1989, the Web of Science reports only 159 cumulative citations using the terms hormesis or hormetic, all appearing from 1982 onward. The hormesis concept had therefore been explored only to a very limited degree through the 1980s. In contrast, in the year 2008 alone the number reached 2,275. So the question maybe asked as to how hormesis emerged from an uncertain and marginalized concept to one that became accepted as real?

The key initial activity derived from a desire of the Texas Institute for Advanced Chemical Technologies (TIACT) based at Texas A&M University to determine whether hormesis was real or not. More specially, Dr. Paul Deisler, a board member of TIACT, wanted TIACT to fund a study to answer this question. His idea led to a grant being given to the University of Massachusetts in 1995. It was the TIACT funding that lead us to create objective evaluative criteria to assess the existence of hormetic dose responses and to the conclusion that hormesis was not only a real and reproducible phenomenon but that is was likely to be very general, being independent of biological model, endpoint measured and chemical class/physical stressor agent (Calabrese and Baldwin, 1997). This research has continued to the present with a progressively expanding database of findings of hormetic dose responses (Calabrese and Blain, 2005, 2009). Specialized studies have been published on numerous receptor systems (Calabrese, 2001a-i), chemotherapeutic agents (Calabrese and Baldwin, 2003b), ethanol (Calabrese and Baldwin, 2003c), inorganic agents (Calabrese and Baldwin, 2003d), immune responses (Calabrese, 2005b), human tumor cell lines (Calabrese, 2005c), numerous neuroscience endpoints (Calabrese, 2008,a-n), plant biology (Calabrese and Blain, 2009) amongst others. These findings have added more support to the conclusion that the hormetic dose response is highly generalizable with broad based applications.

DEVELOPMENT OF A FREQUENCY OF HORMESIS

Even though the above discussed research indicated that hormesis was real and a very general phenomenon, it did not provide a measure of the frequency of hormesis in the toxicological and/or pharmacological literature. Estimating the frequency of hormesis was considered to be of importance for regulatory agencies. For example, different strategies or policies could be developed if the hormetic frequency was <5% versus >40%. Thus, just knowing that hormesis was a real biological phenomenon was insufficient. This lead to an evaluation of nearly 21,000 articles in three toxicology and/or pharmacology journals from their inception to the most recent, assessing all articles with a priori entry and evaluative criteria. It is interesting to note that only 2% of the dose responses satisfied the entry criteria but of those that did, nearly 40% satisfied the evaluative criteria for hormesis (Calabrese and Baldwin, 2001). Thus, for the first time there was documentation of a frequency of hormesis within the published literature.

COMPARING THE THRESHOLD, LINEARITY AT LOW DOSE AND HORMESIS MODELS: WHICH IS MOST FREQUENT?

In general, our research has focused on comparing the hormetic dose response with the threshold dose response for frequency. This is because the endpoints that had been studied in the most appropriate manner (i.e. strongest study designs) have involved non-cancer endpoints. This fact has lead to giving the linear model less emphasis in our publications. In these comparisons the most striking observation is that the threshold dose response model consistently performs very poorly. This has been shown in multiple studies using a wide range of biological models, endpoints and agents (Calabrese and Baldwin, 2001, 2003a; Calabrese et al., 2006a,b, 2008). In contrast, the hormetic model has performed very well in these same head to head comparisons. However, recently there has been the proposal that all agents may induce their toxic effects via a linear, non-threshold manner (White et al., 2008). In our studies that are cited above in this section, it was found that the linear at low dose model, like the threshold dose response model, performed very poorly in our evaluations, thereby not supporting this new attempt to generalize the linear model.

DEFINING HORMESIS

In a broad reading of the general or popularized articles on hormesis, it has often been defined as a low dose beneficial response to a stressor agent. However, Calabrese and Baldwin (2002a) proposed that the dose response definition of hormesis be decoupled from a decision on whether the response was beneficial or not. This was done because it had become obvious to us that the low dose hormetic stimulation could be either beneficial or harmful, depending on the situation. For example, an antibiotic such as streptomycin may stimulate the proliferation of harmful bacteria in an animal while killing the bacteria at higher doses. Thus, at low doses the streptomycin would be helping the bacteria but harmful to the patient while the reverse would be the case at higher doses. A chemical may be seen to display an enhancement of longevity at low doses but decreasing longevity at higher doses. However, whether the increase in longevity for the individual would be beneficial for the species may not be true. Thus, the decision on whether the low dose hormetic response is beneficial or not can be complex and not necessarily immediately obvious.

QUANTITATIVE FEATURES OF THE HORMETIC DOSE RESPONSE

When we initiated research on hormetic dose responses we did not provide overriding consideration to the quantitative features of the dose response. Our thinking was far more qualitative at the early stages of development, that is, was there a low dose stimulation and was it reproducible. However, once data emerged on several thousand hormetic dose responses that were assessed for various dose response parameters it became clear that the most consistent quantitative feature of the hormetic dose response was the magnitude of the stimulatory response. Rarely was it greater than twice the control group. In general, the maximum stimulation for hormetic responses appears to be 30-60% greater than control group (Calabrese and Baldwin, 1998). This feature was consistent across biological models, endpoints and agents tested. This was an important observation since it clarified why hormesis could be difficult to document. That is, since the maximum stimulation was modest it would require the use of rigorous study designs along with considerable statistical power.

With respect to the width of the stimulatory response, this was generally modest as well, typically being about a factor of ten. However, in about two percent of the cases the width of the stimulatory zone was quite wide, exceeding a factor of 1000 (Calabrese, 2008o). These observations have considerable toxicological and clinical implications as one considers the therapeutic zone or zones of exposure to avoid.

Another feature of the hormetic dose response curve is that it was always adjacent to the threshold response. This characteristic would make the upper boundary of the hormetic response very predictable, a factor that could be of considerable value to those involved with risk assessment and therapeutics.

IS THERE A SINGLE MECHANISM FOR HORMESIS?

This has been a common question raised at various conferences held on the topic of hormesis. When one considers that the hormesis phenomenon is extremely general, being independent of biological model, endpoint, and chemical class, it quickly becomes clear that a single proximate mechanism is not possible to account for the diversity of hormetic dose responses. However, there appears to be a common overall strategy of resource allocation within all biological systems, regardless of endpoint measured. The hormetic dose response may quantify how the system allocates resources. This is reflected in the observation that the maximum stimulatory response is typically limited to only 30-60% greater than the control group.

GENERAL HORMETIC MECHANISMS: DIRECT STIMULATION AND OVERCOMPENSATION STIMULATION

Another issue that was not considered in the early evaluative stages of the hormesis concept was whether it occurred via a direct stimulation or via compensatory response. However, this would become an important consideration as will be seen below. My first research experience introduced me to the concept of hormesis but I was unaware of the term or its temporal qualities. I observed that a synthetic growth inhibitor consistently induced a biphasic dose response for growth in Peppermint with a low dose stimulation and a high

dose inhibition (Calabrese and Howe, 1976). Although plant growth was measured weekly the results of greatest interest were those at the end of the study which was typically about six weeks. More that two decades later I read several papers by Tony Stebbing on hormesis which emphasized the importance of the dose-time-response in assessing hormesis (Stebbing 1998). He indicated that initially there would be a disruption in homeostasis (i.e. toxicity), followed by an overcompensatory response which would be seen as a stimulation. This encouraged me to go back to my original laboratory notebooks, re-analyzing the data in the manner suggested by Stebbing. When this was completed, Stebbing's prediction was confirmed. That is, during the initial weeks of the study there was a dose dependent decrease in growth followed by the overcompensation growth stimulation (Calabrese, 1999). This re-assessment was possible because the study design employed many doses and a repeated measures component. The majority of experiments do not include both components, thereby preventing a detailed dose-time-response. In the hormesis database (Calabrese and Blain, 2005, 2009) about 20% of experiments have a dose-time-relationship. These experiments have been important in clarifying that hormetic dose responses may occur via the overcompensation stimulation mechanism. However, we also observed that there were numerous reliable examples in which hormetic dose responses occurred as a result of a direct stimulation, with no initial disruption in homeostasis.

These observations were interesting because they indicated that hormesis could occur by two different modes of action. Despite this clear difference in mechanism, the quantitative features of hormetic dose responses were the same for the direct and the overcompensation stimulation types of hormesis. Since most studies demonstrating hormesis do not contain a time component one is not able to know whether the particular case of hormesis is direct stimulation or overcompensation. The question was raised (and will be addressed later) as to why these two types of hormesis would also display the same quantitative features of the dose response relationship even though they were affected via different mechanisms.

AN HORMETIC MECHANISM STRATEGY

A wide range of drugs has been found to reduce anxiety in rodents by activating one of a variety of specific receptor pathways. Regardless of the drug used and the pathway activated, the quantitative features of the dose responses are similar. Another interesting feature is that the co-administration of anti-anxiety drugs that act via different mechanisms (i.e. activate different receptor pathways leading to the decrease in anxiety), regardless of drug potency, have their combined responses limited by the constraints of the hormetic maxima (i.e. plasticity constraints). This suggests that there is a downstream integration of multiple pathways each of which can facilitate a reduction in anxiety. This downstream integration/conversion suggests a type of carousel model in with the resulting molecular product, that is, the dose response (e.g. analogous to the speed of the carousel) being similar.

HIGH RISK GROUPS

The issue of high risk groups and how they are protected by environmental health standards is an important public health consideration. In 2001 we were challenged by Lave (2001) to explore this issue since our earlier publications of hormesis had been directed to other questions. In a 2002 paper Calabrese and Baldwin (2002b) reported that hormetic dose responses were found to be generally independent of inherent susceptibility. The principal finding was that those at increased risk have their dose response shifted to the left, showing hormesis and toxicity at lower doses than the so-called normal segment of the population. However, in some cases, the susceptible segment of the population is at high risk precisely because it lacks the adaptive hormetic mechanism. Furthermore, the quantitative features of the dose response for those at increased risk are similar to the normal segment of the population. The knowledge of hormesis and differential susceptibility is important for those involved in setting environmental and occupational exposure standards as well as for the pharmaceutical industry which may target the hormetic stimulation when defining the therapeutic zone or when the hormetic zone needs to be avoided due to toxicity concerns.

TOXICOLOGICAL / PHARMACOLOGICAL POTENCY

Agents can widely differ in their potency for producing the same endpoint. Such differences could exceed several orders of magnitude. However, despite such differences in potency there is no difference amongst these agents with respect to the quantitative features of the hormetic dose response nor other qualities of the hormetic response (Calabrese, 2008o). This is an important concept since a very potent agent will display the same quantitative features of the hormetic dose response as a weak agent, but doing so at a far lower dose.

MIXTURES AND HORMESIS

Mixtures have not been extensively studied within an hormetic context. However, there are sufficient data published that permits one to make some tentative general conclusions on how they are handled within an hormetic framework (Belz et al., 2008). Particularly insightful have been the studies of Flood and his colleagues (Flood et al., 1985, 1984, 1983, 1982) concerning the effects of drugs on memory in rodents. These investigators have consistently shown a complex dose response relationship. Most importantly, the maximum extent to which they could increase memory was constrained by the so-called 30-60% stimulation rule. This was the case regardless of whether one or multiple agents were administered. If two or more memory enhancing drugs were administered there could be an additive or greater than additive relationship but this would have to occur at a very low dose, where the response was some distance below the 30-60% physiological performance cap. As the response approaches the maximum, the nature of the interaction would change from greater than to less than additive. In effect, the nature

of the hormetic interaction is principally seen at the level of dose rather than response. These findings indicate that the stimulatory response will be limited to the 30-60% zone but that it may be possible to achieve this response level with a considerably lower dose due to the chemical interaction. Flood indicated that this would reduce the likelihood of experiencing adverse side effects. The concept of mixture responses within an hormetic dose response context is considerably different than that which is typically studied within a toxicological framework. The hormetic interaction has important response constraints whereas this is not the case for standard toxicity endpoints at doses greater than the threshold.

HORMESIS: A QUANTITATIVE INDEX OF BIOLOGICAL PLASTICITY

The most striking feature of hormesis is that the stimulatory response is consistently modest with the maximum response about 30-60% greater than the control value. Since this is the case regardless of mechanism, endpoint and model, pharmacological potency, for mixture responses and for chemical class, it strongly suggests that this response describes the plasticity of biological systems at multiple levels of organization ranging from the cell to the organ to the organism (Calabrese 2008q, 2008r). The findings indicate that this biological response is highly conserved as it is seen from organisms ranging from bacteria to man as well as in plants. These findings have important implications for clinical therapeutics as well as all dimensions of biological performance.

PRE-CONDITIONING IS A MANIFESTATION OF HORMESIS

The term pre-conditioning entered the medical lexicon in 1986 when Murry et al. reported that a brief occlusion of the coronary artery of dogs one day prior to inducing a major myocardial infarction reduced cardiac damage by about 80% as compared to the control group in which only the myocardial infarction was induced. These findings initiated a cascade of research, which was generalized well beyond the cardiac system, yielding similar protective findings. While most of these studies used only one or two types of exposures making it impossible to assess an hormetic explanation, a number of studies have teased out the dose response of the conditioning agent/exposure regiment (Davies et al., 1995; Nicolosi et al., 2008). In these studies the conditioning agent displays an hormetic biphasic dose response, with similar quantitative features of hormesis. The findings clearly indicate that there is an exposure optima with the protection dropping off on either side. If the pre-conditioning exposure is too high then it could further enhance the toxicity of the subsequent toxic or harmful exposure/treatment.

HORMESIS AND THE 21ST CENTURY

In an earlier question/answer it was noted that the vast majority of papers reporting hormetic dose responses are recent, occurring since the year 2000. One major reason for this is that in the mid 1980s there was a major shift toward the use of cell culture and the study of cell lines. The use of cell cultures often have employed 96 cell plates which allow for the assessment of 7-11 concentrations in each experiment. This is 2-3 times more treatment groups than the typical in vivo rodent assay. This was what the hormesis concept required in order to increase the likelihood of it being observed. In 2007 the US National Academy of Sciences (NAS) published a book concerning toxicity testing for the 21st century. Amongst their far reaching recommendations was the eventual elimination of the chronic bioassay and its replacement with well validated in vitro studies using various human cell lines. If these recommendations are followed it suggests that hormetic dose responses will be a central feature of 21st century toxicological findings (U.S.NAS, 2007) as in vitro studies will often employ a larger number of treatment groups across a broader concentration range than would occur with a traditional in vivo toxicological study.

HORMESIS AND BIOLOGICAL PERFORMANCE

The hormetic low dose stimulatory response represents a new concept in toxicology and pharmacology, being a measure of biological performance. This is seen with respect to endpoints such as the plant growth, strengthening bones, improving memory, decreasing anxiety, increasing seizure thresholds, growing hair, attracting neutrophils to sites of infection, decreasing mutation rate and tumor formation and many other responses. The dose response therefore has two response components, that is, the above the threshold response and the below the threshold response. The above threshold response is generally unrestrained as seen with high dose toxicology in which evidence of tissue damage or mutational effects or other toxic endpoints can increase by several hundred or even a thousand or more fold. While there are often pharmacokinetic limits on the induction of toxicity, toxic responses are generally very progressive and have the potential to massively increase. This is not the case with responses below the threshold where the hormetic stimulation becomes manifest.

DRUG BENEFIT LIMITATIONS

When a new and improved drug reaches the market there maybe the assumption that it will produce a greater benefit than older competitive drugs. It will grow more hair, reduce anxiety better, make stronger bones, and boost memory. The hormesis concept indicates that this is not necessarily the case. Hormesis imparts a limit on how much gain there is in the biological system. Many hundreds of endpoints display the same approximate level of modest maximum gain, that is, only in the 30-60% range. Even the vastly more potent drugs will not increase the performance. They simply give the same performance, but at a lower dose. The gain in the system is limited by the constraints imposed by plasticity.

IS HORMESIS RELATED TO HOMEOPATHY?

In earlier writings I have separated hormesis from homeopathy. I even went so far as to say that homeopathy was the equivalent of a scarlet letter on the forehead of hormesis (Calabrese, 2001j). The lay public and even many in the medical profession often confusedly merged the concepts. Hugo Schulz discovered the basic concept of hormesis in the mid 1880s in experiments assessing the effects of disinfectants on the metabolism of yeast. Through a type of convoluted logic Schulz came to believe that he had discovered the explanatory principle of homeopathy. In fact, the studies of Schulz had nothing to do with the concept of homeopathy. However, biomedical investigators in The Netherlands (Van Wijk and Wiegant 1997; Van Wijk et al., 1994) have tried to explicitly design studies that might link the two concepts via what is now called post-conditioning hormesis (Calabrese et al., 2007). These investigators demonstrated that low doses of heat or chemical toxin when given after a stress (i.e., disease process simulation) can amplify the initial response to stress in a hormetic-like fashion. While this research was experimental rather than clinical, it provides a framework for further study. Given legitimate criticisms of the ultra dilutionist wing of homeopathy, it must be emphasized that this research of Van Wijk deals with exposure to stressor agents that can be readily measured and is fully capable of being evaluated within normal biomedical experimental protocols. Unfortunately, this research was published during the mid to late 1990s and has not been continued. Nonetheless, this new experimental framework provides a conceptual vehicle to facilitate the evaluation of some homeopathic treatment strategies within an hormetic context.

HORMESIS AND HARMFUL EFFECTS

When I first started to assess hormetic dose responses little thought was given to the possibility that harmful effects would occur. Most attention was given to whether hormesis was a real, reproducible phenomenon. However, it eventually emerged that the low dose stimulatory hormetic responses could at times lead to undesirable effects. For example, low doses of antibiotics were shown to occur as early as the mid 1940's by FDA researchers to stimulate the proliferation of harmful bacteria. In vivo studies with low doses of penicillin as well as streptomycin enhanced mortality in mice given an LD50 dose of a deadly bacterial strain while preventing death at higher doses (Randall, et al., 1947; Welch et al, 1946). This remains a potentially very significant area of public health research.

Low doses of numerous agents, including anti-tumor drugs, have been shown to enhance the proliferation of tumor cells (Calabrese 2005c). These findings suggest that under certain conditions the administration of anti-tumor drugs to cancer patients may enhance the proliferation of the tumor cells. This is particularly the case for drugs with a long biological half-life. Some anti-tumor drugs used for the treatment of humans, such as the drug suramin, not only display the hormetic biphasic dose response with multiple tumor cell types but also have a rather prolonged period of residence within the human body, taking nearly two months to clear (Kuratsu et al., 1995). In such cases there would be a prolonged period of time during which the drug would be present at very low concentrations. Whether these concentrations would be optimized to enhance tumor cell proliferation is an important question to resolve. The fact that anti-tumor agents can stimulate tumor cell proliferation at low doses within an hormetic context has generally not been widely appreciated by the cancer treatment community that emphasizes the high dose killing portion of the dose response curve.

This concept has been generalized to other areas of cancer treatment, including brain tumors. For example, anti-inflammatory agents such as dexamethesone have been shown to enhance the proliferation of human neuroepithelial brain cancer cells in vitro displaying an hormetic dose response (Kuratsu, 1998; Rutka, 1998; Tabuchi, 1998; Yoshida, 1998). Such findings generated considerable concern amongst brain surgeons who commonly used anti-inflammatory agents in the management of their patients' pain.

Another potential adverse effect caused by the low dose hormetic stimulation may include the enlargement of the prostate gland due to the proliferation of smooth muscles following exposure to cardiac glycosides (Chueh et al., 2001; Abramowitz et al., 2003). The magnitude of stimulation, which is about 20-40%, is likely to have clinical implications in some patients with respect to affecting urination. The condition known as Dupuyteren's Contracture is also likely due to the overproduction of fibroblasts induced by low doses of reactive oxygen, with the response following an hormetic dose response relationship (Murrell et al., 1990).

A number of immune diseases have also been related to the occurrence of a low dose stimulatory response. While a detailed assessment of hormetic responses of the immune system suggested that most would be beneficial, in about 20% of the cases, the low dose stimulatory response could lead to harmful effects, such as certain autoimmune responses including lupus (Bluestein et al., 1979) and tuberculin hypersensitivity (Bramm et al., 1979).

HORMESIS IN DRUG DISCOVERY, DEVELOPMENT AND IN THE CLINICAL TRIAL

Drug discovery, development and clinical trial efficiency could be significantly enhanced if they were guided by principles derived from an understanding of the concept of hormesis. This is the case for drugs designed to kill harmful agents. For example, in screening of agents that may be very effective at killing bacteria, fungi, viruses, yeasts, and tumor cells, it would also be important to know whether these agents might be effective stimulating the proliferation of these organisms. It would also be important to know the biological half life of the drug in humans. Ideally, the drug should be effective in killing the harmful agent, have a low capacity to induce cell proliferation at low doses and have a short biological half-life. Nascarella and Calabrese (2009) have recently demonstrated that there is an inverse relationship between the capacity to kill yeast cells that are models of human tumor cells and the capacity to induce an hormetic dose response. This makes it even more important to be

guided by hormetic principles in the selection of anti-tumor cells. It would be important to know whether this concept could be generalized to the case for harmful bacteria, yeasts and viruses.

The concept of hormesis is central to drug development when the goal of the research is to determine whether the drug can increase human performance (e.g., memory enhancement, bone strengthening). The quantitative features of hormesis will determine the magnitude of the enhanced performance as well as the width of the therapeutic zone. However, it is also doubtful that researchers in these areas are acquainted with the hormesis term, its concept and implications. Of particular concern is the how the hormetic concept can guide and affect response expectations, study design and statistical power features of both preclinical studies and clinical trials.

IS THE HORMETIC RESPONSE MORE DEPENDENT ON THE ORGANISM OR THE INDUCING AGENT?

The question has often been asked as to whether all chemicals can induce hormesis or conversely is the key determinant of the hormetic response the organism. Since all chemicals can induce toxicity, depending on the dose, and hormesis may occur as an overcompensation to a disruption in homeostasis, hormesis would be expected to occur for all agents depending on the experimental context. On the other hand, this is not likely to be the case for agents that induce hormesis via a direct stimulation since these agents are typically going to occur via a receptor mediated pathway activation process.

CHEMICAL STRUCTURE AND HORMESIS

The chemical structural determinants of hormesis is a generally unexplored area of investigation. Nonetheless, several groups have reported that structural factors can be determinants of whether an hormetic response will occur or not. This has been intensely studied in the area of anxiotytic drug development. In these investigations researchers have systematically assessed the presence or absence of an hormetic dose response for each of a large number of highly related chemicals, differing by a single molecular characteristic in a long series of agents. These investigations demonstrated that the hormetic biphasic dose response was reproducibly inducible but it was highly dependent on certain structural characteristics. These hormetic dose responses have the potential to be predicted via SAR methods (Im et al., 1996; Jacobsen et al., 1999, 1996).

HORMESIS AND AVOIDING SIDE EFFECTS

Hormesis is a biphasic dose response that often results from the actions of partial agonists and partial antagonists. Part agonists/antagonists are extremely common, being seen in most, if not all, receptor systems. The use of partial agonists/antagonists will diminish the likelihood of adverse effects while creating a broader dose response range over which the response would occur (Im et al., 1996; Jacobsen et al., 1999, 1996). These two features are extremely important for the survival of the individual. One can imagine the survival implications of individuals affected by adverse side effects, ranging from headaches to dizziness, to seeing double, amongst others. A major factor therefore in evolutionary success is to minimize undesirable side effects of endogenous agonists. As one can see with the modern pharmaceutical world this is not an easy task. However, this could be another critical dimension of hormesis within an evolutionary context.

THE HORMETIC PHARMACY

Numerous adaptationally-based beneficial responses conform to the hormetic dose response. These responses have the capacity to protect vital organs such as the heart, lungs and brain from a host of damaging stresses/conditions. The hormetic response is also manifested via accelerated healing in various experimental systems (Rattan et al., 2009). Hormetic responses are also seen with cognitive improvement, in slowing down the onset of various aging processes and in a plethora of neurodegenerative diseases, as well as in reducing susceptibility to a broad spectrum of infectious diseases (Calabrese, 2008b). Hormesis is also seen in the strengthening of bone, reducing the risks of osteoporosis as well as in treating male sexual dysfunctions and with the capacity to grow hair (Calabrese, 2008p). Research is now being focused on the next generation of pharmaceuticals called hormetic mimetics. These are endogenous or exogenous agents which activate hormetic adaptively beneficial receptor pathways. It is expected that these agents will be translated into life enhancing pharmaceuticals (Smith-Sonneborn, 2008). In short, hormetic effects are a central feature of the modern and future pharmacy.

IS SCIENCE SELF-CORRECTING AND IF SO, HOW EFFECTIVE IS IT?

One of the major revelations of hormetic dose responses is that the scientific community was quick to accept the threshold dose response model and to incorporate it into the entire spectrum of governmental hazard assessment evaluations and in the risk assessment process. The research and regulatory communities accepted its intellectual framework without validating whether this model could accurately predict responses in the low dose zone. Since homeopathy and what we now call "traditional" medicine have been engaged in a bitter conflict for nearly two centuries, the hormetic dose response concept became collateral damage in this social, economic and medical battle (Calabrese, 2005a). This failure to vet the threshold model was largely a consequence of the conflict between homeopathy and traditional medicine. The field of pharmacology, being an important dimension of traditional medicine, aggressively attacked the writings of Hugo Schulz who had proposed that the hormetic biphasic dose response provided the explanatory principle of homeopathy. Since toxicology emerged from pharmacology it adopted the dose response perspective of its parent, without much self initiated investigation. The entire experimental, evaluatory, regulatory

and teaching aspects of toxicology came to adopt this 1930s mantra of the dose response. The system surprisingly was never critical of its assumptions about the threshold dose response but always found ways to marginalize the hormesis concept. This is even the situation today, especially as manifested by directions of grant programs that control many professional activities. Furthermore, governmental regulatory agencies continue to find the hormetic dose response extremely challenging and threatening, even though it should help them perform their jobs of serving the public considerably better.

Of particular concern is that the research community, especially in the toxicology domain, can have their intellectual climate directed by regulatory agency toxicology needs. Thus, those persons who control grant funding will largely control the creative directions of the research community. In this way, the non-critical acceptance of the threshold dose response model has been perpetuated through several generations of pharmacologists and toxicologists, who have simply accepted the assumptions of the handed down threshold dose response model as being correct. The results of such toxicological intellectual indoctrination have led to the present state of affairs. While progress is being made on changing this perspective there are also strong governmental institutional controls over how one should think about the dose response and the ability to discuss and assess it openly. This leads back to the question, is science self correcting? Under normal situation science is efficiently self-correcting with the best ideas eventually emerging. However, when regulatory agencies control the intellectual agenda and funding, the self-correcting nature of science is undermined as we had seen over the past nearly 80 years when it comes to the critical issue of the dose response.

DISCUSSION

In the late 1980s there was strong interest in determining whether hormesis was a real biological phenomenon or simply a statistical anomaly. Even the first conference on radiation hormesis in 1985 (see Health Physics, 1987 vol. 52, issue 5 for the peer-reviewed conference proceedings) failed to resolve the issue as reflected in a subsequent debate on the topic in the journal Science in 1989 by two of the conference leaders (Sagan, 1989; Wolff, 1989). However, the opportunity to more systematically assess the hormetic hypothesis dramatically improved with the creation of the hormesis database (Calabrese and Baldwin, 1997; Calabrese and Blain, 2005, 2009) which has collected and assessed over 8000 examples of dose responses displaying evidence of hormetic dose responses. The database permitted an assessment of questions relating to reproducibility of findings, generalizability across biological models, endpoints and chemical classes, as well as the quantitative features of dose responses and temporal nature of the hormetic response. These initial efforts helped to firmly establish that hormetic responses occurred, were reproducible and not uncommon. Despite this advance there were other questions, especially those relating to the frequency of hormesis in the toxicological literature and the mechanism or family of mechanisms that could account for hormetic dose responses. With respect to the frequency of hormesis this was to require the creation of a new hormesis database, one that had a priori entry as well as evaluative criteria. This effort, which involved a separate evaluation of nearly 21,000 articles, revealed the first frequency of hormesis within the toxicological/pharmacological literature, with a value of nearly 40% (Calabrese and Baldwin, 2001). Furthermore, there was considerable evidence in the pharmacological literature to account for mechanisms by which direct acting hormetic dose responses occurred using agonist gradients via receptor subunits to activate stimulatory or inhibitory pathways (Calabrese and Baldwin, 2001).

One of the key general observations was that the quantitative features of the hormetic dose response were the same, regardless of the biological system, the endpoint that was measured or the agent that induced it. This was a striking general observation that applied to stimulation of tumor cell proliferation, memory enhancement, immune cell stimulation, plant growth, decreases in anxiety and the broad range of other endpoints reported. These quantitative features of the dose response would occur whether the stimulatory response was of a direct or overcompensatory nature. This suggested strongly that the quantitative features of the hormetic dose response were so widespread and general that it may in fact be a quantitative estimate of biological plasticity independent of species.

While the initial emphasis behind the hormetic reappraisal was environmental risk assessment, the data now indicate that this concept far more general, impacting any aspect of biology concerned with dose response relationships. This makes the hormesis concept central to molecular biology as well as pharmacology, toxicology (Hoffmann, 2009), and risk assessment (Scott, 2008, 2007; Calabrese and Cook, 2005).

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RADIATION HORMESIS - A REMEDY FOR FEAR

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ABSTRACT

Personal reflections on radiation hormesis for the past fifty years are presented. The causes of ignoring and rejections of this phenomenon by international and national bodies and by radiation protection establishment are analyzed. The opposition against nuclear weapons and preparations for nuclear war was probably the main factor in inducing the concern for adverse effects of low doses of ionizing radiation, a byproduct of activism against the nuclear weapon tests. UNSCEAR was deeply involved in preparation the scientific basis for cessation of nuclear test, and contributed to elaboration of the LNT assumption, which is in contradiction with the hormetic phenomenon. However, this authoritative body recognized also the existence of radiation hormesis, termed as "adaptive response". The political and vested interests standing behind exclusion of hormesis from the current risk assessment methodology are discussed.

Key Words: hormesis, radiation, adaptive response, hormetic, linearity, risk assessment

I began working with ionizing radiation in 1953, as a medical doctor - radiotherapist at the Institute of Oncology in Gliwice. At that time my colleagues and I were not interested in protecting ourselves from radiation. Our main concern was to cure our patients by irradiating their tumors with high doses while protecting their healthy tissues outside the tumor volume against harmful collateral effects. This approach resulted in a permanent loss of papillary lines on my fingers, and on those of my colleagues. I estimate that my body must have absorbed a dose of some 600 mGy from such professional and from subsequent medical exposures. Perhaps this is why at the age of 82 years I am still active in winter and summer outdoor sports (I must however admit that the very persistence in such activity might be the real cause of its duration). In the early 'fifties at the Institute of Oncology we treated some advanced cases of leukemia with fractionated whole body or hemi body irradiations, up to a total dose of 2 grays, exposing both neoplastic and healthy tissues. The palliative results were positive. I believed that this effect was partly due to the stimulation of the defense system of the patients' healthy tissues, but I did not think of this as being a "hormetic effect". In fact, the term "hormesis" had been coined ten years earlier (Southam and Erlich, 1943) but was not widely used. Hormetic effects were known to exist since the end of the 19th century(Calabrese et al., 1999), and while after World War II they were mentioned in some 20 articles each year (Brucer, 1987), they were clearly out of the mainstream interest of radiologists. Whole- and hemi-body radiotherapy were soon forgotten at our Institute, due to the exaggerated fear of irradiating healthy tissues even with small doses, only recently to regain some recognition (Wojcik et al., 2002).

It was the Cold War period with its massive production and incessant testing of nuclear weapons. Strontium-90 and caesium-137 fallout from atmospheric tests polluted the whole planet and, together with the terrifying prospect of a global nuclear war, induced worldwide radiophobia. People were quite rightly scared of large lethal doses of radiation from local tropospheric fallout, deposited over distances of hundreds of kilometers from the sites of nuclear explosions. But later they also became scared of small doses of radiation arising from the global stratospheric fallout of nuclear tests in the atmosphere. The fear of lethal doses was a highly cherished element of the deterrence value of nuclear weapons, loudly voiced by their owners. One of the more important examples was the excellent handbook of Glasstone, demonstrating the disastrous effects of atomic weapons, published by the United States Department of Defense and the Atomic Energy Commission (Glasstone, 1957). But it was the leading physicists responsible for inventing the nuclear weapons, having realized how dangerous were their inventions, who instigated the fear of small doses. In their noble, wise and highly ethical endeavor to stop preparations for atomic war, and the "hysterical" amassment of enormous arsenals of nuclear weapons, they were soon followed by many scientists from other fields. The general strategy was to attack the crucial component of military nuclear efforts of the time – atmospheric nuclear testing. Later on, this developed into opposition against atomic power stations and all things nuclear. Although the arguments of physicists and of their followers were false, they were effective: atmospheric tests were stopped in 1963 (Rusk et al., 1963), only to be moved underground. However, this was achieved at a price –a terrifying specter of small, near zero radiation doses endangering all future generations had emerged. This specter became a long-lived and worldwide societal affliction, nourished by the linear non-threshold (LNT) assumption, according to which any dose, even that close to zero, would contribute to the disastrous effect. Radiation hormesis is an excellent remedy for this affliction, and it is perhaps for this reason that this phenomenon has been ignored and discredited over the past half century. What happened fifty years ago still influences the current thinking of the decision makers and of those who elect them. Therefore, let us dwell upon it for a while.

In March 1950, over a year before the first American H-bomb explosion on May 8th 1951, Albert Einstein estimated that "*radioactive poisoning of the atmosphere* (by H-bombs) *and hence annihilation of any life on earth, has been brought within the range of technical possibilities*" (Einstein, 1950). In the same year Hans Bethe, the former head of the Theoretical Physics Division of the Manhattan Project, and a major contributor to the development of the Hiroshima- and Nagasaki-type fission nuclear weapons, warned on television that H-bomb clouds *"could annihilate life on earth*" (Anonymous, 2005).

Similar statements were later repeated in innumerable publications, and captured in popular books and movies of the 1950s, such as *On the Beach, Fail-Safe,* and *Dr. Strangelove.* I demonstrated that such statements were unjustified (Jaworowski, 1999). If the whole global nuclear arsenal at its peak of 50 000 warheads and 13 000 megaton explosive power were to be exploded over a few days, the average individual would have received a life-time (70 year) radiation dose of about 55 mSv ensuing from the worldwide fallout, a far cry from the short-term dose of 3000 to 5000 mSv that will most likely kill a human or induce an epidemic of chronic post-irradiation diseases.

Eight years later, Linus Pauling, the chemistry Nobel laureate, virtually repeated what Einstein and Bethe had said, by stating that merely the preparation for thermonuclear warfare (and not the war itself) would destroy most of the planet's living creatures (Pauling, 1958). In a telegram of 1st March 1962 to President J.F. Kennedy, on the effects of nuclear tests, he estimated the genetic effects of small radiation doses from fission products and carbon-14 dispersed by nuclear tests: "*I state that nuclear tests .... would seriously damage over 20 million unborn children, including those caused to have gross physical or mental defect, and also the still births and embryonic, neonatal and childhood death*". Pauling's telegram started with a question: "*Are you going to give an order* (to continue the tests) *that will cause you to go down in the history as one of the most immoral men of all time and one of the greatest enemies of the human race?*" Perhaps the impact of this telegram was reflected in President Kennedy's statement: "*Today every inhabitant of this planet must contemplate the day this planet may no longer be habitable*". For this social activism, four years later Pauling received his Nobel Peace Prize.

Interestingly, two inventors of nuclear weapons were also honored with peace rewards. Andrey Sakharov, the father of the Soviet H-bomb, was awarded the Nobel Peace Prize in 1975. In 1978, Samuel Cohen, inventor of the neutron bomb, was awarded the Peace Medal by Pope Paul VI. In the same year, the next Pope, John Paul II congratulated him: "*Mr. Cohen, I trust you are working for peace*" (Cohen, 2005).

On the other side of the Iron Curtin the Soviets were competing with Americans in mass production and testing of fission and fusion weapons. They also built vast arsenals of conventional weapons, preaching worldwide peace at the same time. In the midst of this arms race in 1958, Andrei Sakharov, the father of the first Soviet H-bomb (1953) and of its next more sophisticated and more powerful version (1955), published an astonishing paper in Russian (Sakharov, 1958). After eleven years this paper was re-published in English in Moscow (Sakharov, 1969), and 32 years later - in the United States (Sakharov, 1990).

Most certainly publication of Sakharov's paper in the Soviet Union would not have been possible without prior consent or instigation of the highest authorities, perhaps as a Soviet peace stage in the Cold War drama. Sakharov's paper revealed two important messages on the hydrogen bomb. The first was a description of the fundamental fusion reactions occurring during the explosion of such a bomb (available for the first time in the open literature of the Soviet block, one year after their declassification by Glasstone), of its neutron flux and of the rate of the ensuing radiocarbon (^{14}C) production in the atmosphere. The second message was the calculation of radiation dose from globally dispersed carbon-14 (0.375 mSv per caput). Assuming a future global equilibrium population of 30 billion people, Sakharov estimated a "collective dose commitment"[1], truncated to 8000 years (i.e. to the approximate life-time of ^{14}C), from radiocarbon and other radionuclides produced or dispersed in the atmosphere by nuclear tests up to about 1958. Sakharov concluded that the dose commitment from the weapons tests would result in 500,000 to one million victims of serious hereditary disorders and cancers. In his calculations Sakharov used the LNT principle, with a risk factor for hereditary effects based on data from *Drosophila melanogaster* fruit fly experiments (Muller, 1954). These and similar data were based on high dose X-, gamma- and beta-ray irradiations, ranging between 2.7 and 43.5 Gy (Oliver, 1930; Muller, 1946), which after extrapolation to zero dose, became a basis for the assumption that mutation frequency increases linearly with dose without any threshold. This assumption was adhered to in many later genetic experiments (Sankaranarayanan and Sobels, 1976; UNSCEAR, 1962).

However, the linearity assumption was not confirmed by early epidemiological surveys of Hiroshima and Nagasaki survivors (UNSCEAR, 1962), nor by later studies (UNSCEAR, 2000; UNSCEAR, 2001), in which no hereditary disorders were found in the progeny of highly irradiated parents. For estimation of carcinogenic radiation effects, studies of somatic cells are more relevant than those on germ cells. The results of early experiments with *Drosophila* male germ cells irradiated with X-rays do not agree with new findings in which somatic mutations in the *Drosophila* clearly showed a threshold around 1 Gy (Koana et al., 2004). Koana et al. also found a threshold (below which no increase in mutation frequency is detected in spermatocytes and spermatogonia) between 0.2 and 10 Gy (Koana et al., 2007; Koana et al., 2004). In the 0.2 Gy dose group and at low dose rate of 0.05 Gy/min these authors observed hormetic effects (40% less lethal mutations than those in sham-irradiated flies).

Over several decades the early experiments on mice carried out at Oak Ridge National Laboratory formed the basis for genetic risk estimates, for which the doubling dose for mosaic mutations was believed to be 1 Gy. Reevaluation of the Oak Ridge data demonstrated that in these experiments the frequency of spontaneous mutations was underestimated. The true doubling dose ranged in fact between 5.4 and 7.7 Gy. As the doubling dose increases, estimates of hereditary risk decrease. Therefore, the estimate of risk to humans based on old experiments using mice is probably at least 5 times too high (Selby et al., 2004; Selby, 1998). After perusal of Selby's revision the United Nations Scientific Committee on the Effects of Atomic Radiation decided that "*the prudent way forward is*

1 Four years later UNSCEAR defined the dose commitment to the world's population as a sum of radiation doses from a practice (for example, a series of nuclear tests) over endless generations and an infinite time period (UNSCEAR, 1962). I argued that this speculative concept, as well as that of collective dose, both related to LNT, have no biological meaning, and obliterate information required for realistic risk assessments (Jaworowski, 1999).

to abandon the use of an entirely mouse-data-based doubling dose estimate" (UNSCEAR, 2001). The Committee cited also the doubling dose in humans as ranging between 3.4 and 4.5 Gy, this being estimated from the Hiroshima and Nagasaki data (a strange conclusion, since Japanese data had shown no adverse genetic effects of bomb irradiation). Yet, the Committee decided that it "*will use the round figure of 1 Gy in risk estimation*".

However, at the time when Pauling and Sakharov announced their estimates of thousands and millions of genetic victims of nuclear tests, UNSCEAR, after three years of deliberation, did a more balanced and competent job in its first report, published at the end of 1958 (UNSCEAR, 1958). It accepted the possibility of zero increase in leukemia incidence – assuming a threshold, and that 150 000 cases would ultimately occur for non-threshold calculations. The Committee's estimation of the ultimate genetic defects was between 2500 and 100 000 cases (UNSCEAR, 1958).

UNSCEAR was established in 1955 by a resolution of the General Assembly of the United Nations. The Committee reports directly to the General Assembly, and its formal terms of reference are strictly scientific. Over its following five decades the Committee had diligently strived at estimating the effects of small radiation doses from all kinds of sources, and became an unquestionable authority on the matter of radiation effects in humans and their environment. However, as appears from the general conclusions of its 1958 report, the Committee was concerned mainly with the effects of nuclear tests, fulfilling a political task: to help in "*the cessation of contamination of the environment by explosions of nuclear weapons*". The effects of high radiation doses in nuclear war were never a subject of UNSCEAR studies. Later the emphasis of the Committee's work was on other types of exposure, and its publications became a foundation for the international radiation protection recommendations and national regulations.

In 1958 the Committee presented an ambivalent approach to LNT, which reflects the mixed opinion of its members on this subject. This is exemplified by conflicting statements such as: on theoretical grounds, if one ionization suffices to cause the effect, then "*this sort of effect has no threshold – which means that any dosage, however small, is effective in producing some alteration. On the contrary, if several ionization events are needed, the dose effect curve is sigmoid. In this case there is a threshold*". For mutational hazards the Committee was less prone to accept a threshold, stating that "*biological effects will follow irradiation, however small is amount*". However, it acknowledged that "*the studies of mutations in bacteria, Drosophila, and mice do not extend as low as the background radiation, and much uncertainty remains*".

The cautious approach of the Committee is best seen in the general conclusions of the 1958 report, among which one can read that "*Many effects of radiation are delayed; often they cannot be distinguished from effects of other agents; many will develop once a threshold dose has been exceeded...*", or "*the possibility cannot be excluded that our present estimates exaggerate the hazards of chronic exposure to low levels of irradiation*". Support for the LNT approach was most strongly worded in a *votum separatum* of the Soviet delegation (UNSCEAR, 1958). The criticism of LNT in this document was less explicit, but not among some of its authors. Professor W.V. Mayneord, one of the leading radiologists and head of the British delegation at the first session of UNSCEAR in March 1956, stated later "*I have always felt that the argument that because at higher values of dose an observed effect is proportional to dose, then at very low doses there is necessarily some 'effect' of dose, however small, is nonsense*" (Mayneord, 1964).

A similarly cautious approach was evident in the next 1962 UNSCEAR report. While stating that "*the relationship between dose and effect at cellular and subcellular levels does not give any indication of the existence of threshold doses and leads to the conclusion that certain biological effects can follow irradiation, however small the dose may be*", the Committee also observed that "*When dose effect relationships are studied at higher levels of organization, ... it is now being increasingly realized that the situation may be more complex, since many factors play a part between the occurrence of the primary event and the final manifestation of radiation damage*" and that therefore "*a simple mathematical relationship is unlikely to apply*".

In its first report of 1958 the Committee noticed adaptation and the possibility of repair of genetic material, but had not discussed these effects. In that document hormesis is clearly evident in a figure presenting survival times of gamma-irradiated mice and guinea pigs at dose rates of 5 mGy per week (page 162), and also in a table showing leukemia incidence in the Hiroshima population, which was lower by 66.3% in survivors exposed to 20 mSv, compared to the unexposed group (p. 165). This evidence of radiation hormesis was not commented upon. Since then, the standard policy line of UNSCEAR and of international and national regulatory bodies over many decades has been to ignore any evidence of radiation hormesis, and to promote LNT philosophy.

I tried to understand the reasons why was such a policy continued long after its original aim, i.e. stopping atmospheric tests of nuclear weapons, has been achieved. It seems to me that the driving force was (and still is) the vested interests of the radiation protection establishment and of the antinuclear power lobby, both concerned that demonstration of the beneficial effects of small radiation doses, and thus of the existence of a threshold for harmful effects occurring near this dose region, will destroy their *raison d'etre*. Refraining from studying or even acknowledging the existence of the phenomenon of hormesis may be regarded as non-scientific and political influences in the field of radiological sciences (Taylor, 1980); (Weinberg, 1972; Weinberg, 1985).

Ionizing radiation is very widely used in many walks of life. Only in its medical applications, some 330 million people are being exposed every year at low doses for radiodiagnostic purposes, and another 5 million undergo radiotherapy at high doses (UNSCEAR, 2000). Since its discovery until 1992 there were only 402 fatal victims among medical professionals (Molineus et al., 1992), and between1944 and 2001 only 134 fatalities occurred in all radiation accidents (Toohey, 2002). This indicates that radiation is a rather innocuous and not very lethal agent, a fact that the public is not aware of well enough.

Major human activities, including nuclear incidents, increase the radiation exposure of the global population to very low levels above natural background, well beyond those at which any hormetic effects may be apparent. For example, in the record year of 1963, the maximum average annual radiation dose to the global population from nuclear test fallout was 0.113 mSv (UNSCEAR, 2000). Until 1982 in its reports to the General Assembly, for comparing radiation exposures from the most important man-made and natural sources, instead of radiation dose units, the Committee used "units of days equivalent exposure to natural sources". I protested many times against this practice, and finally radiation units were used, but never in graphic form. Years ago I prepared a figure comparing these exposures in sievert units, based exclusively on data from UNSCEAR documents (Figure 1). At several sessions I proposed that the Committee publish such a figure in its report to the General Assembly, but to no avail. The official reason for rejection was the difficulty in making this figure understandable to laymen, but the real explanation offered to me on the side was: "*Visual perception is the most effective, and such a figure may make the politicians at the UN General Assembly think that the vast effort and resources spent on radiation protection of the population are excessive, and the very existence of UNSCEAR might be at stake*".

Reluctance to demonstrate clearly how unimportant is any radiation hazard to population from nuclear industry, the Chernobyl accident, nuclear explosion tests and medical irradiation, in relation to the broad range of natural radiation exposure, at which no adverse health effects were ever observed, reflects a "vested group interest" approach. However, what is published, are staggering and terrifying values of "collective doses" from these same sources (for example 2 330 000 man Sv per year from X-ray medical examinations – UNSCEAR, 2000), which are meaningless results of multiplying of innocuous tiny individual doses by 5.8 billion people. A "collective dose" of 14 000 000 man Sv per year from natural sources is not given for comparison and balancing in the public's mind of millions of man-made man-sieverts.

I was disappointed that the phenomenon of hormesis was ignored in all UNSCEAR documents since its first report. Therefore, in 1980, as chairman of the Committee, I suggested that it was the duty of UNSCEAR to peruse the large body of publications on radiation hormesis, some 1200 articles, published since the beginning of the century, to assess whether this phenomenon is real, and if so, how might it influence the methodology of risk estimates. A large review on this literature had already been published by then (Luckey, 1980), and the Committee had it in its library. The proposal was supported only by the delegation of Poland, and UNSCEAR rejected it. Every following year I repeated this proposal in vain, until after the Chernobyl accident of 1986, in 1987, it finally gained support, first from the representatives of France and Germany, and then from other delegations. Seven years later UNSCEAR published a report, rubberstamping the existence of the phenomenon of radiation hormesis, termed as "adaptive response" (UNSCEAR, 1994).

It was difficult for the Committee to overcome its own prejudices on radiation hormesis, and to produce a balanced report. Along the way, the Committee rejected two rather one-sided drafts of the report, prepared by the late Dr. Hylton Smith, the Scientific Secretary of ICRP, a body which strongly supported LNT and rejected hormesis. However, working for a few years on the report, Dr. Smith changed his initially negative approach to radiation hormesis, and finally produced an excellent, unbiased treatise on this yet unfathomed matter, demonstrating his scientific integrity. When the Committee finally endorsed the report, from the rostrum came this comment of UNSCEAR's Scientific Secretary: "*We are now in total disarray!*". During the Committee's 1995 session, the IAEA observer, Dr. Abel J. Gonzalez, reacted in a more vehement mood, scorning UNSCEAR for publishing its 1994 report, and arguing that this report contradicted the freshly issued Agency's Interim Edition of the "International Basic Safety Standards" (IAEA, 1994). My answer was that UNSCEAR is an independent body, our terms of reference being not regulations but science. I continued that scientific integrity of the Committee and its separation from non-scientific influences are essential for preserving UNSCEAR's role as the objective authority on the matter of ionizing radiation, and that it is not the role of IAEA to instruct UNSCEAR on its duties.

UNSCEAR's 1994 report had a considerable impact on science, reflected among others in the BEIR VII (BEIR-VII, 2005), and French Academy of Sciences - National Academy of Medicine (Tubiana et al., 2005) documents, supporting research on radiation hormesis. It also influenced regulatory bodies, as reflected by publications of the former ICRP chairman (Clarke, 1999) and by his proposals of scrapping some standards and principles based on LNT, such as "*Collective dose*", presented at the 10th International Congress of IRPA at Hiroshima in 2000. These proposals were rejected by the Congress (Webb, 2000), although many speakers supported them, claiming that LNT assumption is incorrect in view of the hormesis phenomenon (Anonymous, 2000). But the implications of hormesis for radiation protection include more issues than were discussed at this Congress, such as dose additivity, tissue weighting factors, radiation weighting factors, the sievert definition of effective dose and dose rate effectiveness factor (DDREF) and ALARA, all closely intertwined with the LNT approach (see e.g. (Cook and Calabrese, 2006; Mitchell, 2006).

During the fourteen years which had elapsed since the UNSCEAR report on adaptive response was issued, several new professional scientific journals and societies have emerged, covering the rapidly developing field of hormetic science. Important new information on radiation hormesis has also appeared in a great number of peer-reviewed publications. At the 2007 session of UNSCEAR the Polish delegation proposed that the Committee should critically review this new matter, which is of vital importance for the philosophy and practice of radiological protection. As in the past, the Committee did not agree to include such a study in its current program of work. I hope that, as in the past, the Committee will soon reconsider this issue.

Threshold or no threshold - that is the question, posed in the UNSCEAR 1958 report, and still unresolved. The no-threshold principle, seemingly simplifying radiation protection procedures (or its

bureaucracy), has not only enormously increased their cost, but most importantly, is the culprit who created the universal fear of low levels of ionizing radiation. Among the disastrous consequences is the present lack of public acceptance of nuclear energy, the only realistic means of satisfying the future needs of humanity.

Proponents of the no-threshold philosophy often claim that one can never, with any finite experiment, prove that a given environmental factor is totally harmless. Thus, even if no effect is observed, such as is the case with hereditary disorders in Hiroshima and Nagasaki, one can only state that there is a certain probability that in fact there is no effect. Then the precautionary principle is invoked, and unrealistically low exposure standards are coined. To claim this position with a clear conscience, LNT protagonists should first falsify the elementary model of Feinendegen-Polycove (Feinendegen, 2005) which provides a logical and mathematical basis for radiation hormesis.

The hormesis concept transcends that of a dose threshold. In the absence of hormesis, the existence of a true threshold might be impossible to demonstrate rigorously because of the statistical difficulty of absolutely proving equality of effect in an epidemiological study. If however a deficit is observed in the irradiated population, as is the case in hormesis, there may be a statistically significant difference at an acceptable confidence level (Webster, 1993). The very existence of radiation hormesis phenomenon proves the existence of radiation thresholds and falsifies LNT. This is why hormesis is the best remedy for the mass psychological affliction called radiophobia, and, by the same token, this is why it is ignored by the influential part of the radiation protection establishment, against a vast factual evidence and the benefit of society.

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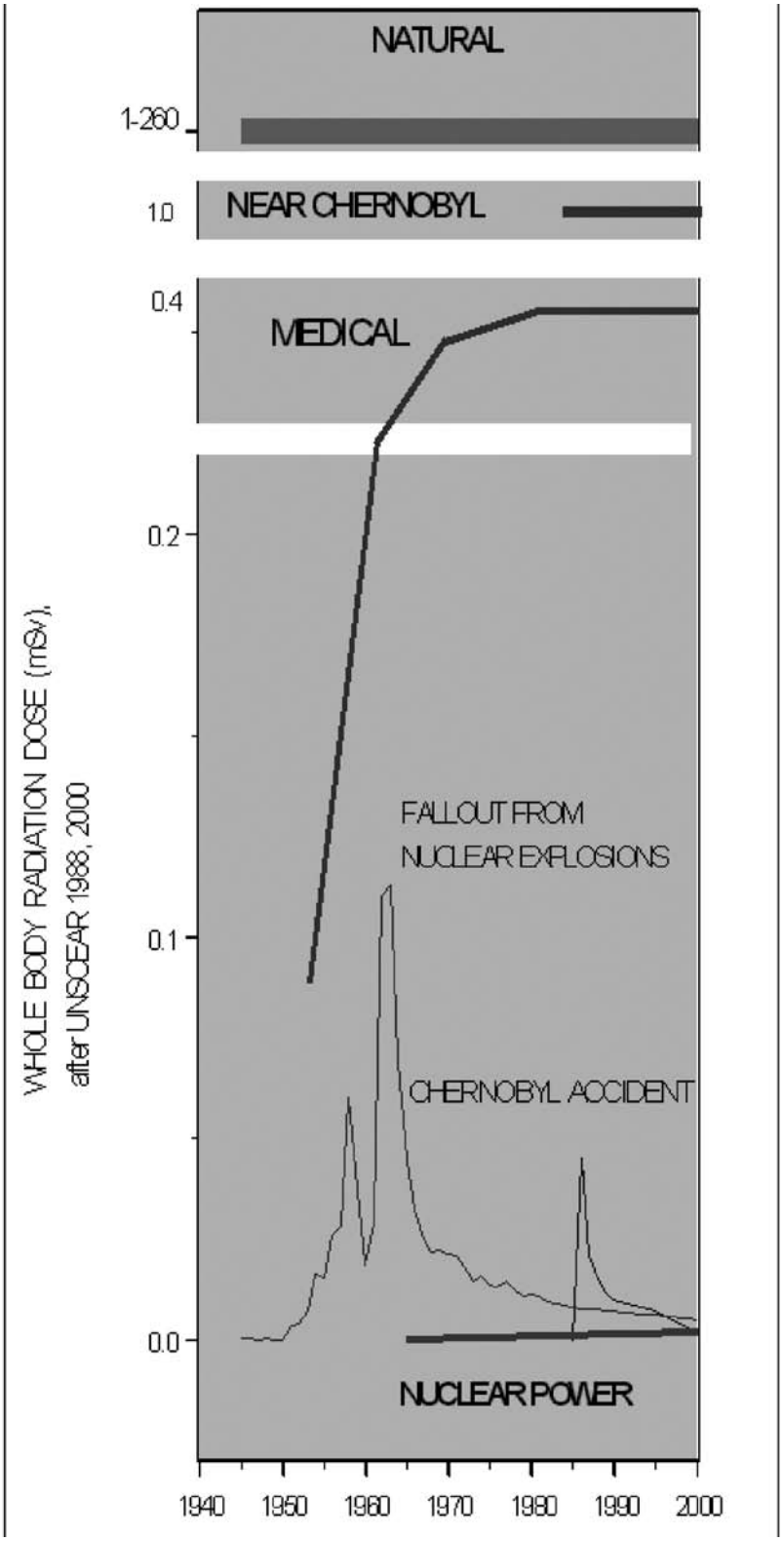
FIGURE 1.

Exposures of global population from major radiation sources, and of inhabitants of regions highly contaminated by radioactive fallout after Chernobyl accident. After (UNSCEAR, 1988; UNSCEAR, 2000).



WHAT DOSE METAPHOR?

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ABSTRACT

The concept of hormesis, or low-dose U-shaped responses, is now well established in toxicology and pharmacology, but requires development in medicine and therapeutics. In doing so, care must be taken to not confuse metaphorical and chemical uses of the term hormesis. Low dose, continuous adaptive responses are fundamentally different than conventional pharmacology, and they may improve the scientific underpinning for complementary medicine, nutrition and lifestyle therapies.

CONCEPT ERRORS AND CLINICAL PROGRESS IN HORMESIS

I first came across the *BELLE Newsletter* and the concept of hormesis about 12 years ago when I was Director of the Office of Alternative Medicine at the National Institutes of Health. At that time, we were looking for scientific frameworks under which we could conduct research on the areas called complementary and alternative medicine (CAM). The conventional framework was that the effects reported from these practices were all due to placebo, psychological context, expectation and belief. While certainly the so-called placebo or meaning and context effects contributed to a number of the observations in these fields, such a framework was not adequate to explain many of the observations from these practices and provided a rather uni-dimensional approach to the CAM field. [1] The basic problem was that most CAM substances had little specific chemical effect. That is, treatments from many CAM approaches such as herbs, homeopathy and acupuncture were too low dose. The active ingredients in most herbal preparations for example, are quite low by the time they get digested, absorbed and distributed. Homeopathy is based on a tenet of giving low doses of substances. Acupuncture involves very small and subtle stimulations of the body as does massage and manipulation. Thus, when I came across the writings in the *BELLE Newsletter* about the biological effects of low-level exposures, it seemed an opportunity to explore a possible mechanism of some complementary and alternative medicine practices on a more solid scientific basis. Thus, I was pleased to be invited to the BELLE Advisory Board, which I did after my assignment at NIH was over. Since then I have continued to try to bring the clinical perspective to the discussion and debate around hormesis.

Largely due to the heroic efforts of Dr. Ed Calabrese and his colleagues, as well as others in the scientific field, widespread, biological support for hormesis has been well established. Most of the initial work involved documentation and analysis of biological data from the perspective of low-dose effects. Such low-dose or U-shaped effects have now been shown to occur across a number of phyla and biological phenomena and influence many fundamental cellular and physiological mechanisms of relevance to medicine and health care. These include immuno-modulation, endochronological effects and cancer. [2-4] More recently a summary of these effects in neuroscience is being compiled by Dr. Calabrese and colleagues.

Still, the direct relevance and application in the clinical field has remained elusive. This is partly due to the fact that the concept of hormesis and most of the data arises from toxicology and pharmacology and very little attention has been paid to their application within the clinical realm. At the same time, Dr. Calabrese and the BELLE groups have expanded to create the new peer-reviewed multidisciplinary journal Dose Response and the Hormesis Society in a way that brings in multiple disciplines from the bench to the bedside to the boardroom. This has stimulated a rich discussion and increasing adoption of these concepts. The recent publication of the consensus around hormesis terminology and its use across disciplines has helped further that discussion. [5]

However, there are risks from too broad an application of the hormesis concept. Recently Calabrese published an article linking the concepts of hormesis, adaptive response, preconditioning and the Yerkes-Dodson law. [6] These "converging concepts" risk muddying the water by mixing mechanistic phenomena (for example, adaptive response and pre-conditioning in toxicology and immunology respectively) and the more metaphorical concept in which the task and the psychological complexity of a task as an informational construct is equivocated to a physical chemical dose. As Dr. Calabrese points out the Yerkes-Dodson law framework is "analogous to situations in pharmacology and toxicology in which U-shaped dose responses commonly occur." [6] The risk here is that metaphorical concepts such as this are viewed as equivalent to the chemical U-shaped curves found in toxicology and pharmacology. To lump them together as different variations of hormesis confuses rather than clarifies the picture. To argue, as Dr. Calabrese does that the "Yerkes-Dodson law is a special case of hormesis" would require that the more classical observations of hormesis in toxicology be explained in informational rather than chemical terms. To my knowledge that is not how this concept has or should be used. As we move forward into the next decade of hormesis and dose response research, let's make sure that the frameworks for describing and defining hormesis and dose response in terms of both symbolic and chemical concepts are clearly differentiated. Otherwise, confusion will reign.

Another example of how a too widespread application of the concept of hormesis is confusing involves use of the term xenohormesis. In one case the xenohormesis hypothesis postulates that small amounts of chemicals induce stress resistance and therefore longevity when

manipulated by dietary restriction. [7] On the other hand the same term, xenohormesis, has been used to explain how dietary chemicals may induce toxic effects at low doses by mimicking molecules in the diet that facilitate function. [8]

Ultimately, clarity of the concepts in hormesis in terms of its chemical and informational constructs need to be differentiated. Otherwise, the term hormesis will be so diluted and widespread that it will become equivalent with cellular signaling and risk losing its value as both a scientific and heuristic concept. Regardless of its use, I would recommend that at least part of what we examine in relationship to hormesis is its practical application within the clinical setting.

Examples of the use of hormesis in both chemical and informational terms exist. For example, we have shown that low doses of glutamate delivered intravenously can mitigate the neurotoxic effects of high doses released from stroke. The timing, dose and relationship to the pathological and recovery processes is crucial for its therapeutic effect. [9] In the symbolic and informational context, stress desensitization has been shown to be one of the few truly effective therapies for the mitigation of post traumatic stress syndrome. [10, 11] However, again, the details of the timing, application and sensitivity of subjects to the exposure are crucial to produce benefit.

Certainly much more needs to be explored in terms of the relationship of both these symbolic and chemical effects to help us build a scientific understanding of how dietary and lifestyle interventions produce benefit and harm. Recent studies that attempt to isolate the purported therapeutic benefits of certain dietary constituents have generally showed no effect when tested in randomized placebo control trials.[12-15] Clearly, a better understanding of how to apply diet and nutritional therapies also is related to timing and sensitivity of subjects. A recent review by Chen, et al, shows that Vitamin A could prevent acute lower respiratory tract infections in children. [16] Generally vitamin-A was of benefit, however, only in those with poor nutritional status. Likewise a recent study of low birth weight in populations taking multivitamin supplements showed some benefits at certain doses but again mostly in those with poor nutritional status. [17]

These and other studies indicate that food, nutrition and ultimately dietary supplements are unlikely to work in a manner similar to pharmacological agents, in which high doses of isolated components are used. It's more likely that dietary and many lifestyle interventions, including interventions involving dietary supplements and the manipulation of macro and micro nutrients, involve low dose adaptive responses over repeated and long periods. Thus, developing a science that links the hormetic concept to therapeutic interventions will require studies that examine the effects of multiple low dose and probably synergistically interacting substances. Those approaches are just beginning to be applied in the area of nutrigenomics [18] and genetics, [19] and such studies could lay a scientific foundation for many complementary and alternative medicines as well as open up new fields for therapeutic interventions when mechanisms are compatible with adaptive responses in biological processes. This then could provide us with a rational approach to understanding if and when so-called natural products, in this case those within the hormetic dose response range, may be safer than those that go outside that range. Over the next decade, let's hope that the *Hormesis Society* and other groups active in this area can explore and apply these concepts for the improved alleviation of suffering and the treatment of disease.

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BIOLOGICAL EFFECTS OF LOW LEVEL EXPOSURES TO IONIZING RADIATION: THEORY AND PRACTICE

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ABSTRACT

This paper briefly reviewed recent reports on the epidemiological and experimental data on low dose radiation effects which support the concept of radiation hormesis. These reports point to the possibility of existence of a threshold dose in cancer induction by ionizing radiation and in some cases the occurrence of hormetic effects with stimulation of host defense mechanisms. The possibility of the use of low dose radiation in cancer treatment to improve the outcome of conventional radiotherapy was raised by citing previous reports on experimental studies which showed increased efficacy in tumor control with significant reduction of total dose of radiation when low dose radiation was used in the combined treatment protocol.

INTRODUCTION

The concept of hormesis has gradually been accepted in the field of toxicological and radiological sciences. The first International Conference on Radiation Hormosis held at Oakland CA, USA in 1985[1] and TD Luckey's book "Radiation Hormosis" (1991)[2] have given great impetus in stimulating research work on biological effects of low level exposures to ionizing radiation at molecular, cellular, tissue and systemic levels. The scientific data in radiation biology in this aspect accumulated in the last 20 years are very convincing. With the accumulation of scientific evidence supporting the concept of radiation hormesis as a general phenomena in radiological sciences, the problem of its possible application in the field of health care has become more and more pressing. This article briefly reviews publications in recent 5 years concerning the beneficial health effects of low level exposures to ionizing radiation and possible application of low dose radiation in the treatment of cancer.

BASIC RESEARCH

DNA damage induced by ionizing radiation, directly or via ROS, is considered to be an important step in the development of various lesions including cancer formation. Recent studies have confirmed previous observations on stimulation by low dose radiation (LDR) of natural defense mechanisms including anti-oxidant formation and repair of DNA double strand breaks (DSBs).[3] Using γ-H2AX as a measure of DNA-DSBs it was found that after low dose radiation growing human fibroblasts could repair DNA-DSBs completely to the level of unirradiated control.[4] Observations on human lymphocytes after CT scan of thorax or abdomen with radiation doses in the range of 3-30 mGy showed that the γ-H2AX foci increased dose-dependently in this dose range and the lesions were completely repaired within 24 h.[5] Of course, the disappearance of γ-H2AX foci does not necessarily mean that no misrepaired lesions remian. And these misrepried lesions may later on become the source of genomic instability and neoplastic transformation. Therefore, the influence of LDR on neoplastic transformation has become a subject of concern. Recent experimental studies have shown that LDR could reduce the frequency of mutations induced by high dose radiation, and LDR could even decrease the rate of chromosome inversions produced by high dose radiation when acting after the latter.[6,7] Further experiments showed that LDR reduced the rate of neoplastic transformation to below spontaneous level.[8] Low energy (28 kVp) low dose radiation used in mammography does not increase the frequency of neoplastic transformation at doses of 0.5 to 220 mGy, and doses of 0.5 to 11 mGy reduce the neoplastic transformation rate to below spontaneous level.[9] There existed a threshold even for the neoplastic transformation induced by high energy protons and doses <100 mGy of this high energy radiation could suppress the transformation rate.[10] The mechanisms of the low dose effect have not completely been clarified, and preliminary studies suggest that it may be related to DNA repair, since 3-aminobenzamide, an inhibitor of poly-ADP-polymerase, could reverse the suppressive effect of 50 mGy on neoplastic transformation.[11]

Recent research has refuted the concept that cancer is a disease of single cells. It is now clear that the development of cancer depends on intercellular reactions in the tissue and is influenced by defense and adaptive mechanisms in the complex organism. The intercellular reactions in the local tissue involve fibroblasts, immune and inflammatory cells as well as cytokines related to them, especially the action of TGF-β (transforming growth factor-β), adhesion molecules (integrins) in the promotion of cancer development.[12-15] Recent studies have shown that the integrity of normal tissue structure plays an important role in the suppression of the carcinogenic effect of oncogenes. For example, it has been observed in 3-D culture of mammary cells that the integrity of the mammary epithelial structure suppresses the carcinogenic effect of c-Myc gene and the maintenance of this tissue integrity is related to LKB1 gene,

so that deletion of LKB1 leads to destruction of the integrity of tissue structure and appearance of cancer-like cells.[16] Therefore, it is envisioned that "normal cells unite against cancer" and, if they fail, cancer cells will "hijack" normal cells (including fibroblasts, immune cells, etc.) to favor their proliferation and invasion. High doses of radiation change soluble and insoluble elements of tissue microenvironment and thus affect cell phenotype, tissue structure, intercellular physical relations and signal transduction. The mechanisms of these microenvironment changes induced by high dose radiation include persistent action of chronic inflammation and TGF-β.[17] At the same time high doses of radiation suppress the immune surveillance against cancer while low doses of radiation activate anticancer immune functions.[18,19]

Radiation bystander effect is a phenomenon which has attracted the interests of radiobiologists. The first observation was made with microbeams of α particles irradiating a small portion of cultured cells resulting in damage in the unirradiated "bystander " cells. The mechanism of such effects is related to signals passed from the irradiated cells to the unirradiated cells directly via gap junction-mediated intercellular communication between cell contacts or signal molecules released from the irradiated cells into the microenvironment, e.g., NO, TGFβ, etc. It means that not all lesions in the cells are produced by the traversal of radiation through the "target". With the discovery of this phenomenon it was once argued that the linear no-threshold model may underestimate the risk of health effects of radiation. However, when cultured C3H10T1⁄2 cells were pre-irradiated with 20 mGy of γ-rays 6h before the hit of α particles, an adaptive response was observed manifested as increase of survival by 75%. It was thus thought that α particles chiefly cause damage and low dose γ-rays induce adaptive response.[20,21] There are also recent studies showing that LDR-induced bystander effect may be manifested as apopstosis, thus eradicating the cells with genomic instability and lowering the frequency of neoplastic transformation. Such a phenomenon was called apoptosis-induced protective effect.[22,23] Furthermore, signals from low dose-irradiated non-transformed cells could cause apoptosis of transformed cells.[24] Therefore, radiation bystander effect can either cause damaging effect or give rise to adaptive response, depending on the actual condition. There also exists a threshold for the induction of bystander effect, for human skin cells the threshold dose of γ-rays being 2 mGy. The threshold dose for different species may vary greatly, and genetic or epigenetic background may be more important than the irradiation dose in the induction of bystander effect.[26,27] For example, bystander signals for apoptosis could be induced by irradiating C57BL/6 mice, but not CBA/Ca mice.[28]

CANCER PREVENTION BY LOW LEVEL RADIATION

Recent reports on epidemiological surveys have shown beneficial health effect of low level exposures to ionizing radiation expressed as decreased cancer mortality and/or all-cause mortality as well as increased life span (longevity). Examples of these are the Hanford downwind inhabitants 50 years' survey,[29,30] the Chernobyl contaminated area 20 years' survey,[31] the US nuclear shipyard workers study (NSWS) of more than half a century,[32,33] the British radiologists 100 years' observation[34] and the British nuclear workers 51 years' study.[35,36] These population studies are supported by laboratory research. It was found that for the induction of thymic lymphoma in normal mice by γ-rays there existed a threshold dose of less than 1 Gy since doses within 1 Gy of γ-rays did not increase the occurrence of lymphoma above the basal level, and after irradiation with 5 Gy the incidence of lymphoma increased to 12.5%. Even in SCID mice, which have defect in DNA-DSB repair and immune deficiency, there exists a threshold dose of 0.1 Gy for induction of thymic lymphoma. Irradiation with this dose does not increase the occurrence of lymphoma above the spontaneous rate of 31.7% and irradiation with 0.25 Gy and 2 Gy increases the occurrence rate of lymphoma to 51.4% and 80.6%, respectively.[37,38]

It was further found that low dose or low level radiation could suppress the carcinogenic effect of high dose radiation. C57BL/6J mice exposed to fractioned doses of whole-body irradiation with 1.75 Gy X-rays once a week for 4 consecutive weeks with a total dose of 7.0 Gy resulted in occurrence of thymic lymphoma in 43.3% of mice within 6 months. When each fractioned dose of 1.75 Gy was preceded by whole-body irradiation with 0.075 Gy with an interval of 6 or 12h, the incidence of thymic lymphoma decreased to 15.1% and 17.1%, respectively ($P<0.05$), while unirradiated mice and mice receiving 4 doses of whole-body irradiation with 0.075 Gy alone did not develop thymic lymphoma within 6 months of observation.[39] When the same protocol was applied to C57BL/6J mice with the fractioned dose increased to 1.8 Gy (total dose 7.2 Gy) instead of 1.75 Gy (total dose 7.0 Gy), 90% of irradiated mice developed thymic lymphoma in 9 months, and when each high dose was preceded by 0.075 Gy, the incidence of thymic lymphoma decreased to 63%.[40] If the preceding low dose was replaced by continuous low level ^{137}Cs γ-irradiation at the dose rate of 20 μGy / min beginning 35 days before the start of the fractionated high dose and continued for 450 days, the incidence of lymphoma further decreased to 43%, while the low level radiation alone for 450 days did not cause development of thymic lympjoma. Continuously irradiated mice showed no loss of hair and a greater body weight than unirradiated controls.[40] The mechanism of the suppressive effect of low dose radiation on the carcinogenesis caused by high dose radiation is apparently related to an adaptive response induced by low dose radiation manifested as reduction of DNA damage caused by high dose radiation as well as activation of immune surveillance induced by low dose radiation.[39,40]

OPTIMIZATION OF CANCER RADIOTHERAPY WITH LOW DOSE RADIATION

Radiotherapy is one of the most commonly used clinical treatments for cancer. However, the potential for tumor control with radiotherapy must always be carefully balanced with the risk for normal tissue damage.[41,42] Large doses of radiation may over-stimulate the secretion of pro-inflammatory cytokines, including IL-12, IL-18 and

others, with the danger of promoting cancer invasion and metastasis.[12,13,43] In addition, tumor cells outside the immediate field of radiation exposure or that have metastasized to distant sites are not destroyed by local irradiation used in conventional radiotherapy. In some cases of more advanced disease, such as non-resectable lung cancer, radiotherapy in combination with chemotherapy may improve the treatment result to some extent, but the toxicity is not easily tolerated. Therefore, it has become an important issue in radiation oncology to seek for measures to decrease local radiation dose and increase anti-tumor effect. It was found that whole-body irradiation with low doses given before implantation of cancer cells (B16 melanoma and Lewis lung cancer) in mice caused retardation of tumor growth, prolongation of survival time, lowering of mortality rate and reduction of pulmonary metastasis.[44] On the basis of these observations experimental studies with the proper use of whole-body X-irradiation with low doses in combination with conventional radiotherapy were designed for the treatment of cancer in mouse models.[45] A mouse model of Lewis lung cancer was established by subcutaneous implantation of cancer cells and treatment was started 10d after cancer implantation. The protocol of local radiotherapy with 5 Gy X-rays in each session with 3 sessions in one week for two consecutive weeks (a total dose 30 Gy) caused significant suppression of tumor growth (curve B in figure 1 as compared with the untreated control in curve A). When the second and third local doses of 5 Gy in each week was substituted by whole-body irradiation with 0.075 Gy (a total dose 10.3 Gy in 2 weeks), the same degree of suppression of tumor growth was achieved as shown in curve C which overlapped with curve B. That is to say, with substitution of 4 large local doses with 4 low doses given as whole-body irradiation the same therapeutic effect was obtained at about 1/3 of the total dose.

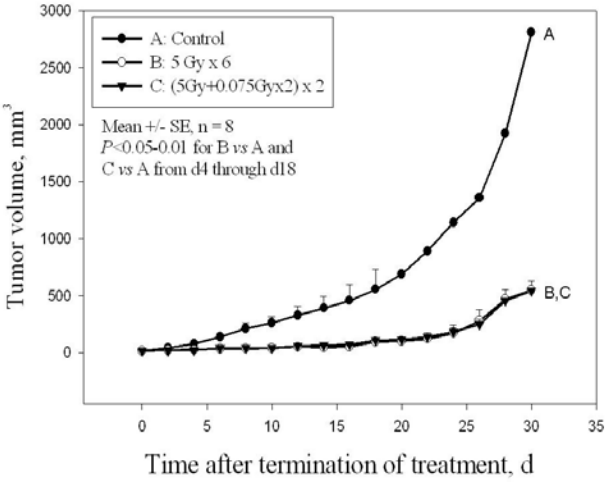

Figure 1 Lewis lung cancer in C57BL/6J mice treated by a combined regimen of local radiotherapy with 5 Gy sessions plus whole-body irradiation with low doses (adopted from reference 45)

Another protocol with 2 Gy x 6 in 2 weeks was tried to see if further improvement of treatment efficacy could be realized by combination of conventional local radiotherapy with whole-body irradiation with low doses. As seen in figure 2, 2 Gy x 6 in 2 weeks (a total dose 0f 12 Gy) could not efficiently control the tumor growth (curve B in figure 2 as compared with curve A which is the control with no treatment), while substitution of the second and third doses of local irradiation with whole-body irradiation with 0.075 Gy in each of the 2 weeks (a total dose of 4.3 Gy), tumor growth was significantly slowed down (curve C in figure 2). That is to say, by substitution of 4 local doses of 2 Gy with whole-body irradiation with 0.075 Gy, therapeutic efficacy was increased with a reduction of total dose by 2/3.

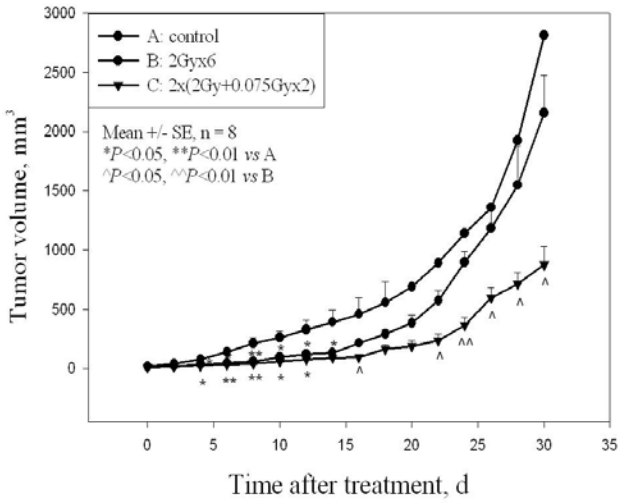

Figure 2 Lewis lung cancer in C57BL/6J mice treated by a combined regimen of local radiotherapy with 2 Gy sessions plus whole-body irradiation with low doses (adopted from reference 45)

Table 1. Comparative changes in tumor growth and progression in different groups of mice treated with different protocols of gene radiotherapy after implantation with Lewis lung cancer cells

Parameter	Group A	Group B	Group C	Group D	Group E
Mean survival time	100	121.2	161.2$^{(1,2)}$	157.7$^{(1)}$	194.1$^{(1,2,3,4)}$
Average tumor weight	100	60.8$^{(1)}$	38.3$^{(1)}$	32.7$^{(1,2)}$	17.8$^{(1,2,3,4)}$
Pumonary metastasis	100	83.3$^{(1)}$	59.5$^{(1)}$	39.9$^{(1,2,3)}$	20.9$^{(1,2,3,4)}$
Intratumor angiogenesis	100	87.9	76.2$^{(1)}$	45.7$^{(1,2,3)}$	30.9$^{(1,2,3,4)}$

Group A: tumor control with no treatment; Group B: 2Gy x 6; Group C: 2 x (2Gy + 0.075Gy x 2); Group D: 2 x (E18B + 2Gy x 3); Group E: 2 x (E18B + 2Gy + 0.075Gy x 2). Mean survival time was calculated from groups of 8 mice in each group at the end of 8 weeks from beginning of treatment. Average tumor weight, pulmonary metastasis and intratumor angiogenesis were from groups of mice, 6 in each, sacrificed 18 d after termination of treatment. All values are calculated with reference to group A as 100%. (1) $P<0.05$ *vs* A, (2) $P<0.05$ *vs* B, (3) $P<0.05$ *vs* C, (4) $P<0.05$ *vs* D. (E18B is the abbreviation of plasmid Egr-mIL-18-B7.1)

Other measures could be added to the protocols mentioned above to further increase the efficacy of cancer control. Gene therapy is one example. It is known that the early growth response 1 (Egr-1) gene is

very sensitive to ionizing radiation. Recombinant plasmids can be constructed with anticancer genes placed downstream of the promoter of Egr-1 gene in order that doses as low as 0.05 to 0.1 Gy of radiation could activate the expression of these molecules to up-regulate anticancer activity.[46,47]

It can be seen from data in table 1 that as judged from the mean survival time, average tumor weight, pulmonary metastasis and intratumor angiogenesis, there was significant improvement when low dose radiation was combined with conventional radiotherapy (compare group C with group B), and intratumor injection of the radiosensitive plasmid Egr-mIL-18-B7.1 (E18B) further increased the treatment efficacy (compare group D with group B and group E with group C). Group E in which low dose radiation was superimposed upon gene radiotherapy showed the most marked efficiency in cancer control. In this group a reduction of total radiation dose to 1/3 of control is accompanied with marked increase of treatment efficacy as shown by doubling of survival time and reduction of tumor weight and metastatic foci to around 1/5 of the control.

CONCLUDING REMARKS

The biological effect of low level exposures to ionizing radiation is a problem of much public concern. The most important health effect related to ionizing radiation is cancer risk. Ionizing radiation at medium to high doses could lead to increase in cancer incidence. However, the cancer risk of low level exposures to ionizing radiation has long been a problem of debate. When BEIR I report was released in 1972 recommending the use of a linear model for estimating radiation risks, UNSCEAR VI questioned its validity in the same year. In 2005 US National Academy of Science released the BEIR VII report and French National Academy of Science and Academy of Medical Science published a joint report on estimation of the carcinogenic effects of low doses of ionizing radiation.[49,50] The former document insisted on using the LNT model for estimation of risk for low and very low doses though it recognized the uncertainty of such judgment, while the latter questioned its validity based on recent advances in the research on biological effects of low level exposures to ionizing radiation.[51,52] In a 2007 updaie on the website of US DOE LDR Research Program support was given to the viewpoint of the French joint report according to recent advances made in experimental studies under the support of this Research Program [53]. As briefly reviewed in the present paper there has been accumulating evidence both from human population surveys and animal experiments pointing to the existence of a threshold dose for radiation carcinogenesis or even beneficial health effect from low level exposures to ionizing radiation.

The use of low dose radiation in combined regimens of cancer therapy was briefly examined with a few experimental examples indicating the possibility of improvement of treatment efficacy using properly planned protocols with the inclusion of low dose radiation. The experimental findings cited in the present paper showed that low dose whole-body irradiation in combination with local radiotherapy could improve the tumor control in mouse lung cancer model, and introduction of the radiosensitive pEgr-IL-18-B7.1 plasmid into the tumor could further promote the treatment efficacy. It is important to note that such an improvement in treatment efficacy was accompanied with a reduction of total radiation dose to about 1/3 of that in the conventional radiotherapy regimen. These experimental findings may set the stage for developing rational clinical protocols in cancer treatment.

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CHANGING CHALLENGES AND PARADIGMS

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ABSTRACT

Change comes as a surprise because things do not happen in a straight line. Concepts often evolve haphazardly, reacting to specific events. Assumptions are made but are not challenged, sometimes for political or social expedience. It has long been recognized that the dose makes the poison. Concepts of the relationship evolved from both events and the availability of exploratory tools. There are consequences to risk aversion. The general concept of Hormesis is perhaps not unexpected. The acceptance of multiphasic dose-responses has the potential to unleash additional and productive insights into this relationship. The activities of BELLE and it's Newsletter provide an excellent example of what can be achieved when dogmas are challenged by the accrual of information that has not been previously examined to see whether additional insights are possible. A forthcoming challenge will be the critical examination of all the inputs and assumptions that will be used in the increasing sophistication of biological modeling.

Key Words: hormesis, hormetic, biphasic, risk assessment

THE WORLD IS DIVIDED INTO PEOPLE WHO THINK THEY ARE RIGHT (ANON)

Fifty years ago I was researching some effects of agents used in anesthesia where the 'dose' was what was put in the syringe and the effect was assessed directly on the subject. Consumer toxicology was in it's infancy, evolving from pharmacology and emphasizing doses that were without measurable effect (or adverse effect). There was no Society of Toxicology or other group interested in risk assessment. The FDA had issued the 'Gray Book' – less than half an inch thick – describing the appraisal of chemicals and drugs. About fifteen years earlier two compounds emerged that saved many millions of lives prior to their potential effects being fully investigated. Indeed, a lengthy regulatory process at that time would have led to millions of deaths. Penicillin had defied the efforts of Florey and Chain to produce testable amounts until finally there was sufficient for injection into a single mouse by John Barnes (later head of the MRC Toxicology Unit). The mouse survived and soon there were sufficient amounts to treat a few individuals with life-threatening infections. Penicillin became a key element in reducing deaths from wounds in World War Two.[1] The other compound that saved many millions of lives is DDT. Again, the first large 'toxicology' experiment involved the application to American troops in Italy facing an outbreak of typhus. Malaria was also a major source of morbidity and mortality in the Pacific zone. After the war, the potential for DDT to control mosquitoes and malaria was exploited by U.S. Public Health authorities. Malaria was still endemic in the U.S.A., particularly in the Mississippi basin.[2] Toxicology was being driven by pragmatic responses to major health issues. Thalidomide slipped through the net. There was not a comprehensive requirement for examining reproductive endpoints in many countries. The use of statistics in experiments and epidemiology was also not universal. The 1956 landmark paper of Sir Richard Doll and Bradford Hill concerning smoking was a major turning point for human disease investigations.[3]

The comprehensive testing of chemicals for carcinogenicity was not yet a requirement by the FDA. However, by the late fifties the FDA showed in two year studies with comparatively small groups of animals that DDT might induce liver tumors. Public opinion was galvanized by Rachel Carson and was one of the factors leading to the formation of the U.S. Environmental Protection Agency. The other, often unrecognized, event was the 1960 recommendation by James Lovelock the eminent scientist and environmentalist ('Gaia') to Lord Rothschild, then head of Research in Royal Dutch/Shell that an electronic capture detector device that he had developed, coupled with gas-liquid chromatography would be a significant advance in the measurement of organochlorine compounds.[4] Overnight the limits of detection were lowered by 2-3 orders of magnitude and 'no-residue' applications suddenly gave measurable residues and evidence of environmental contamination. Regulatory agencies were now confronted with the need to make judgments on the safety of these residues.

One of the first actions of the Environmental Protection Agency was to seek the cessation of the use of DDT and dieldrin. While the focus on DDT related to environmental effects, the Agency, together with the Environmental Defense Fund moved from Cancellation Hearings to Suspension Hearings on dieldrin that could be rapidly completed. A key issue was how to determine an acceptable intake for a compound that caused tumors in animals. Mantel proposed a linear model that utilized a probit unit per log increment in dose. He concluded that this was sufficiently conservative to include all the dose-response data that was then available. The concept of linearity was subsequently developed by Kenny Crump and others into the linearized multistage model that has dominated toxicological dogma for the last three decades. While linearity was initially considered for carcinogens, it spread to other endpoints. There remains a regulatory dichotomy. The EPA has regarded liver tumors as indicative of probable human carcinogenicity, whereas the FDA allows the sale of several classes of very widely used drugs that produce a similar response, sometimes in both rats and mice.

My initial interest in hormesis arose from articles by Harold Boxembaum and Pat Neafsay who utilized data from a large mouse study that we had conducted on dieldrin to demonstrate an apparent hormetic response (see ref 5). I was already interested in the literature on aging and the use of the Gompertz-Makeham (G-M) model

that was commonly utilized in that sphere and that had been used by Pat Neafsay. Following a presentation by Bob Sielkin to a group of epidemiologists it dawned on us that they and animal-based risk assessors used entirely different mathematical approaches due to the way data is developed. Bob proposed that in epidemiology every individual could be regarded as a unique dose group in terms of dose and time. He developed the approach to determine whether potential nonlinearities existed in the age or non-age component.[5] This allowed a more refined analysis of epidemiology information. One apparent reason for rejecting the widespread use of the Gompertz-Makeham model, apart from the fact that is nearly two centuries old, is that at extreme ages the data diverges from the model in that the annual mortality risk remains stable. However, at that stage the remaining population does not represent the attributes of the initial cohort, but rather a unique subset and the deviation actually provides valuable insights.

Modeling has now become part of our national life, driving the forecasting of every dimension of our future, including weather, global warming, economic and health trends. The use of sophisticated models only became practical with the advent of readily available electronic computing about thirty years ago. Among the advances has been the investigation of non-linear, self-organizing systems involving feedback mechanisms that are common in biology. Thus, it has become possible to explore the nature of multi-phasic dose-responses. On a cautionary note, I find that many papers now utilize statistical packages that may not be transparent, providing an illusion of a comprehensive analysis but lacking the thoughtful comprehension of the nature of the information being analyzed. Elsbeth McKay from Australia commented in the January 5th 2008 issue of the New Scientist 'automated thinking tools tend to block people's capacity to see or know the broader context of the problem they face'.

Our exploration of a variety of modeling issues coincided with the spear-heading of the concept of hormesis by Ed Calabrese. It soon became a natural union of interests. Initially the meetings that he organized might be characterized as the exploration of an interesting concept, but needing supporting data. Ed has remarked that "the concept of hormesis may invoke negative judgment by those involved with the practice of medicine as well as those involved with reducing exposures to harmful agents via regulatory activities."[6] The medical hesitancy was related to the possible confusion with homeopathy, while the hesitancy was shared with many in the environmental community who felt that any deviation from linearity was against an almost religious belief that any exposure was bad by definition. A senior member of the EPA Cancer Assessment Group once remarked to me that the Agency was not interested in chemicals that might reduce the risk of cancer. This is also reflected in the wording in the 1986 Guidelines concerning risk estimates that are unlikely to be greater than the upper bound estimate and may be as low as zero – with no acknowledgement of the possibility of less than zero.

Ralph Cook remarked 'We all perceive only what we expect to perceive".[7] His historical paper is worthy of review – he concluded that "The biological effects of the low-level exposures (BELLE) initiative does not dismiss findings that have already been obtained in valid biological research. It incorporates them, accepting the tested observations at high levels, but questions the assumptions related to low level exposures and offers alternative theory: low level exposures may produce paradoxical effects." The BELLE Newsletter provided an informal, readable and timely mechanism for publishing a variety of high quality papers covering a wide range of relevant issues.

A defining moment for BELLE was the support given from Dr Holland's Institute for the Advancement of Chemical Technology at Texas A & M University that allowed Ed with the support to conduct an extensive literature review to define the potential universality of the concept of hormesis. His exhaustive literature analysis revealed many examples in varied systems, suggesting that there is a phenomenon that should be considered in estimating dose-responses. It wad quickly realized that there are issues of measuring such effects in animal studies which have limited dose levels and numbers of subjects per dose.

What is truly remarkable is the emerging acceptance of non-linearity and multiphasic dose-responses. When Ed Calabrese began his journey I gave him a near zero chance of changing the opinions prevailing in the 70's and 80's. However, by his persistence, diligence and organizing abilities, Ed has enlarged the concepts of dose-response that in turn must be reflected by the evolution of the design of experiments. In the BELLE Newsletter and succeeding publications Ed has fostered the input from a wide variety of sources and has allowed a full and frank discussion of the issues. While each change may be incremental, over time progress has been dramatic. The long-term benefits to society may be great if a more flexible, but science-based understanding of risk estimates leads to a more focused reduction of risks.

My congratulations to the BELLE Newsletter and to Ed Calabrese as the instigator and editor.

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