

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 multi-disciplinary 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 nutrigenomics¹⁸ 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 1985¹ 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 remain. And these misrepaired 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,