HET

Human and Experimental Toxicology
29(4) 271–273

DOI: 10.1177/0960327110363975
het.sagepub.com
SAGE

What dose metaphor?

Wayne B Jonas

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 its 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

Samueli Institute, Alexandria, Virginia, USA

Corresponding author:
Wayne B Jonas, Samueli Institute, 1737 King Street, Suite 600, Alexandria, VA 22314, USA.
Email: wjonas@siib.org

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 preconditioning 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 us 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 not likely to work in a manner similar to pharmacological agents, in which high doses of isolated components are used. It is 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 to repeated and multiple signals. 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 signals. 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 complex systems. 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 us 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.

References

1. Moerman D, Jonas WB. Deconstructing the placebo effect and finding the meaning response. *Ann Intern Med* 2002; 136: 471-476.
2. Calabrese EJ. Cancer biology and hormesis: human tumor cell lines commonly display hormetic (biphasic) dose responses. *Crit Rev Toxicol* 2005; 35: 463-582.
3. Calabrese EJ. Hormetic dose-response relationships in immunology: occurrence, quantitative features of the dose response, mechanistic foundations, and clinical implications. *Crit Rev Toxicol* 2005; 35: 89-295.
4. Calabrese EJ, Baldwin LA. Hormesis: U-shaped dose responses and their centrality in toxicology. *Trends Pharmacol Sci* 2001; 22: 285-291.
5. Calabrese EJ, Bachmann KA, Bailer AJ, Bolger PM, Borak J, Cai L, et al. Biological stress response terminology: Integrating the concepts of adaptive response and preconditioning stress within a hormetic dose-response framework. *Toxicol Appl Pharmacol* 2007; 222: 122-128.
6. Calabrese EJ. Converging concepts: adaptive response, preconditioning, and the Yerkes-Dodson Law are manifestations of hormesis. *Ageing Res Rev* 2008; 7: 8-20.
7. Lamming D, Wood J, Sinclair D. Small molecules that regulate lifespan: evidence for xenohormesis. *Mol Microbiol* 2004; 53: 1003-1009.
8. Bland J. What role has nutrition been playing in our health? The xenohormesis connection. *Integrative Med* 2007; 6: 22-24.
9. Jonas WB, Lin Y, Tortella F. Neuroprotection from glutamate toxicity with ultra-low dose glutamate. *Neuroreport* 2001; 12: 335-339.
10. Hogberg G, Pagani M, Sundin O, Soares J, Aberg-Wistedt A, Tarnell B, et al. Treatment of post-traumatic stress disorder with eye movement desensitization and reprocessing: outcome is stable in 35-month follow-up. *Psychiatry Res* 2008.
11. Bisson JI. Post-traumatic stress disorder. *Occup Med (Lond)* 2007; 57: 399-403.
12. Gruber C, Wendt M, Sulser C, Lau S, Kulig M, Wahn U, et al. Randomized, placebo-controlled trial of Lactobacillus rhamnosus GG as treatment of atopic dermatitis in infancy. *Allergy* 2007; 62: 1270-1276.
13. Dalgard C, Christiansen L, Jonung T, Mackness MI, de Maat MP, Horder M. No influence of increased intake of orange and blackcurrant juices and dietary amounts of vitamin E on paraoxonase-1 activity in patients with peripheral arterial disease. *Eur J Nutr* 2007; 46: 354-363.
14. Walker TB, Altobelli SA, Caprihan A, Robergs RA. Failure of *Rhodiola rosea* to alter skeletal muscle phosphate kinetics in trained men. *Metabolism* 2007; 56: 1111-1117.
15. Tepaske R, te Velthuis H, Oudemans-van Straaten HM, Bossuyt PM, Schultz MJ, Eijsman L, et al. Glycine does not add to the beneficial effects of perioperative oral immune-enhancing nutrition supplements in high-risk cardiac surgery patients. *JPEN J Parenter Enteral Nutr* 2007; 31: 173-180.
16. Chen H, Zhuo Q, Yuan W, Wang J, Wu T. Vitamin A for preventing acute lower respiratory tract infections in children up to seven years of age. *Cochrane Database Syst Rev* 2008 (1): CD006090.
17. Shankar AH, Jahari AB, Sebayang SK, Aditiawarman, Apriatni M, Harefa B, et al. Effect of maternal multiple micronutrient supplementation on fetal loss and infant death in Indonesia: a double-blind cluster-randomised trial. *Lancet* 2008; 371: 215-227.
18. Subbiah MT. Nutrigenetics and nutraceuticals: the next wave riding on personalized medicine. *Transl Res* 2007; 149: 55-61.
19. Motter A, Gulbahce N, Almaas E, Barabasi A. Predicting synthetic rescues in metabolic network. *Mol Systems Biol* 2008; 4: 1-10.