Hormesis: Improving Predictions in the Low-Dose Zone

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Abstract This chapter explores the historical foundations of hormesis, including the underlying reasons for its marginalization during most of the twentieth century and factors that are contributing to its resurgence and acceptance within the toxicological and pharmacological communities. Special consideration is given to the quantitative features of the hormetic dose response, as well as its capacity for generalization. Based on subsequent comparisons with other leading dose–response models, the hormesis dose response consistently provides more accurate predictions in the below threshold zone. It is expected that the hormetic dose response will become progressively more useful to the fields of toxicology, pharmacology, risk assessment, and the life sciences in general, especially where low-dose effects are of interest.

Keywords Dose–response relationship · Threshold model · Biphasic dose response · Homeopathy · Inverted U-shape · Adaptive response · Nonmonotonic dose response

Introduction

The discipline of toxicology and its offspring, risk assessment, have as their central pillar, the dose–response relationship. Nearly every fundamental initiative in these fields is centered on this concept. Beliefs about the dose response affect how experiments are designed, what animal models may be selected for study, the

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types of endpoints or diseases assessed, assumptions concerning mechanisms that may account for adverse effects, and how to predict responses, that is, to extrapolate to low-dose exposures to which humans may be exposed. These activities have led to the establishment of large numbers of environmental health standards by the US Environmental Protection Agency (US-EPA) for contaminants in air, water, and soil. The same dose–response methods have also been used by the Occupational Safety and Health Administration (OSHA) to establish industrial health exposure standards and by the Food and Drug Administration (FDA) to protect the public from adverse effects from thousands of drugs and food additives used by society. Likewise, the private sector pharmaceutical industry has used the dose–response relationship as its own central pillar in the design and conduct of essentially all preclinical investigations and clinical trials of vast arrays of approved drugs and those in the evaluation pipeline.

Dose Response: Historical Foundations

These agencies, organizations, and, indeed, the entire biomedical community have built their approaches for assessing the effects of chemicals and pharmaceuticals on the long-standing belief that most, if not all agents, follow a threshold dose–response relationship. This means that at doses above the threshold, biological responses (whether beneficial or harmful) occur, whereas below the threshold the dose is considered too dilute for biological effects to be induced. This belief in the threshold model started nearly a century ago [1–4] became "institutionalized" and has been long taken for granted that it correctly predicts how agents affect all types of biological systems, with no meaningful exceptions [5, 6].

Hormesis: Its Name and Origin

While the above discussion describes past and present dose–response assumptions of the scientific and regulatory communities concerned with the health effects of chemicals and drugs, the core belief in the threshold model has come under severe challenge over the past decade based on reams of data showing that reproducible biological effects often occur at doses below toxic and/or pharmacological thresholds, changing the dose–response relationship from a "threshold" to one with biphasic properties, that is, a low-dose stimulation and a high-dose inhibition [7]. This biphasic dose response is called hormesis (from the Greek meaning to excite), having been so named in 1943 by Chester Southam and John Ehrlich [8], then forestry researchers at the University of Idaho, who observed that extracts from the red cedar tree could inhibit fungal growth at high concentrations while stimulating it at lower concentrations [9, 10].

Historical Blunders

The idea that the fundamental nature of the dose response may be biphasic, that is, hormetic in nature, has a long history. In fact, one can trace its initial formulations back to the late 1880s based on studies in northern Germany by Hugo Schulz [11, 12], a physician and academic pharmacologist, who reported such biphasic dose responses when assessing the effects of various disinfectants on yeast metabolism. However, a problem arose when Schulz, who had a long personal and professional interest in homeopathy due in large part to family friendships [13], thought that his findings provided the underlying scientific foundation for this controversial medical practice. He quickly linked up with leading homeopaths, who were seeking academic credibility, becoming an intellectual leader within this group over the next four decades. Schulz argued that below toxic doses of homeopathic medications induced adaptive responses that enhanced the capacity of patients to resist various diseases and that most agents would be expected to display biphasic dose–response relationships [14].

Since homeopathy was engaged in a prolonged, intense, and very acrimonious competition with what is now called "traditional medicine," Schulz and his dose–response theories became the object of scientific ridicule and became marginalized by leaders in the European medical community, especially well-known, accomplished, and influential pharmacologists such as Alfred J. Clark, chair of pharmacology at Edinburgh. These efforts by Clark and others attempted to link Schulz with the more extremist elements, that is, the high dilutionist wing of the homeopathy field, making him and his biphasic dose–response theory collateral damage in the homeopathy-traditional medicine culture "war" [5]. These efforts to discredit Schulz and therefore his scientific ideas were as successful as they were disingenuous. Lacking in the attacks on Schulz was any acknowledgment that the high dilutionist wing of homeopathy was nonrepresentative of this medical body, since it represented only a very small minority within that medical practice [5, 15]; however, it was easy to attack the extreme positions of this Hahnemann-inspired small minority and then color the entire body of practitioners, including Schulz, with the same brush. Secondly, numerous examples of dose responses similar to those reported by Schulz by other credible scientists with no linkage to homeopathy were never cited in the highly influential writings of Clark [4] (see earlier literature as reviewed in [16–22]).

The guilt by association label that the hormesis concept acquired was unfortunate for the fields of toxicology, pharmacology, and, indeed, all disciplines concerned with dose–response relationships. Hormetic dose–response relationships should not have been a pawn in an economic competition between two medical systems. Hormesis, a dose–response phenomenon that displays a low-dose stimulation and a high-dose inhibition (Fig. 1), with specific quantitative features (as will be discussed in greater detail below) is not the "special" dose response of any medical system, but a scientific concept with important biological implications. Whether such biphasic dose responses could be objectively established and shown to be reproducible was the key issue, a point missed in the battle of medical titans of the early decades of the twentieth century. Nonetheless, the historical foundations that determined which dose response would dominate the twentieth century were determined less by science than by power and politics.

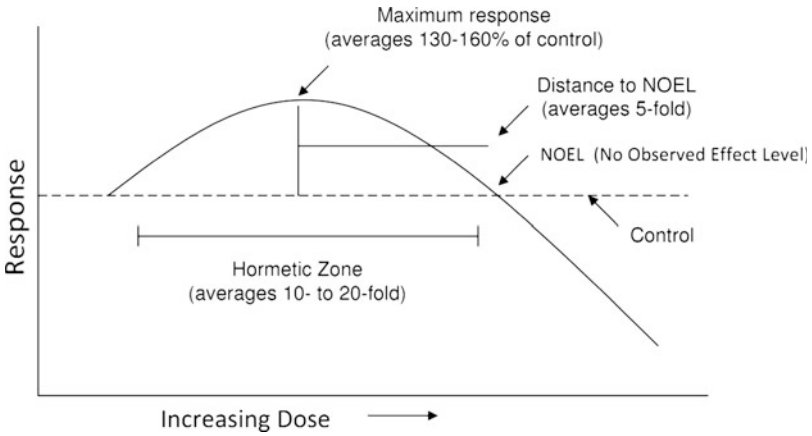

Fig. 1 Dose–response curve depicting the quantitative features of hormesis

Having for all practical intents "killed" acceptance and credibility of the biphasic (later to be named hormesis) dose–response model of Schulz, Clark and the broader pharmacology community made the case for an alternative dose–response model to guide the toxicological and biomedical sciences, and this was in large measure how the threshold model was born and established. It soon became institutionalized in the 1930s during a period of concept consolidation by the scientific and regulatory communities [4]. The entire public health and medical frameworks became based on this foundation, and it remains so even today. The only exception has been in the area of radiation and chemical carcinogenesis in which the threshold model was forced to give way to linearity at low-dose modeling [23, 24] due to society's fear of cancer even though the scientific foundations of the low-dose linear modeling remain impossible to validate low risk estimates (i.e., $1 < 1{,}000$) [9, 10].

Resurgence of Hormesis

By the early 1980s, numerous scientific advances and regulatory conditions had created a framework that would lead to a reexamination of the threshold model and to the current resurgence of interest in hormesis. First, the implementation of linearity at low-dose modeling for cancer risk assessment by US-EPA in the early 1980s based on the recommendation of the National Academy of Sciences (NAS) Safe Drinking Water Committee in 1977 [24] brought enormous new costs to industry since the acceptable exposure standards required cleanup activities to achieve extremely low concentrations. Many in the industrial sector felt such extraordinary remedial activities lacked biomedical justification, and therefore, there was a need to challenge the US-EPA low-dose linearity approach for regulating carcinogen exposures; their initial strategy proposed the replacement of linear at low-dose modeling with the threshold dose–response model since it was likely that all agents, including carcinogens, acted

via thresholds. However, statistical assessments, based on the limited data of individual animal bioassay experiments, could never adequately distinguish the linear from the threshold model. In such cases, the US-EPA would always favor (i.e., default to) the more conservative model, which would be the linear approach.

Realizing that they could never "win" using the threshold model challenge approach, tactics were changed, thinking that the hormesis model might be successful since it could be more readily differentiated from the linear at low-dose model, if only there were data to support it. Thus, in an ironic twist of fate, the extremely conservative approach of the US-EPA for assessing risks from exposures to low doses of carcinogens led to a reexamination of the hormesis dose–response model, its occurrence, frequency, reproducibility, underlying mechanisms, and applications to toxicology and risk assessment. In fact, the first such conference on hormesis was held during August 1985 in Oakland, CA, with a focus on radiation. The peer-reviewed proceedings of that meeting were subsequently published in *Health Physics* in 1987 (see [25]). This meeting indirectly encouraged a series of research-related activities which greatly promoted the hormesis initiative. Secondly, the rapid transition to *in vitro* toxicology and alternatives to whole animal testing also markedly accelerated in the early to mid-1980s. This led to the evaluation of large numbers of toxic chemicals and drugs on a wide range of biological models in which multiple concentrations could be efficiently and concurrently tested on well plate readers that could accommodate far larger numbers of doses/concentrations than traditional whole animal tests (e.g., 10–11 concentrations using 96-well plate readers as compared to the 2–3 doses used in most whole animal studies). This provided an experimental vehicle to efficiently test agents over a broad range of concentrations, thereby providing a framework to evaluate hormetic concepts and hypotheses.

These activities and the efforts of many other researchers with *in vivo* test protocols have led to the creation of a large hormesis database of many thousands of dose responses, all satisfying rigorous evaluative criteria based on study design, magnitude of stimulation, statistical significance, and reproducibility of findings [26, 27]. A second database was also created in order to establish the frequency of hormesis in the toxicological and pharmacological literature [28–30]. These findings indicated that hormetic dose responses are widespread, very generalizable, being independent of biological model, the endpoint measured and the chemical class or physical stressor studied. The frequency of hormetic responses approached 40% using rigorous a priori entry and evaluative criteria, leading to the suggestion that this frequency may underestimate its actual occurrence.

The hormetic dose–response model was also tested in fair head-to-head comparisons with the threshold dose response to assess which model could better predict responses in the critical below threshold dose zone. In three major tests, the hormetic model far outperformed the threshold model [28, 29, 31–34]. The hormetic model displayed a very good capacity to predict low-dose responses with no known limitations. However, the long-revered threshold model was a disappointing failure in each test. These findings are important because they demonstrated that the model used as the basis of all regulatory agencies dealing with noncarcinogenic agents has a critical failing. It simply did not make accurate predictions where it counts most for the public health, that is, in the low-dose zone.

Quantitative Features of Hormetic Dose Responses

The quantitative features of the hormesis dose response are consistent across all biological models and endpoints measured, thereby making it a very specific type of biphasic dose–response relationship. This is particularly the case with respect to the magnitude and width of the stimulatory responses and the relationship of the stimulatory response to the toxicological threshold [27]. Of importance is that the hormetic stimulation is strikingly and consistently modest, being in the percentage rather than in the fold range. That is, the maximum hormetic stimulation is typically about 30–60% greater than control values, rarely exceeding the control by twofold (Fig. 1). The width of the stimulatory response is usually over a 10- to 20-fold range, although in about 5% of the more than 8,000 cases assessed the width of the stimulation has exceeded some 1,000-fold. The cause of this variability in the width of the stimulation is uncertain but might be related to heterogeneity of the test population. The consistency of the stimulatory response to the toxic threshold is also important since it provides a quantitative linkage to the traditional toxicological threshold and therefore permits the hormesis concept to be consistently integrated into standard risk assessment methods. It also permits all past risk assessments to be reinterpreted within a hormetic context [31, 35–37].

The quantitative features of the hormetic dose response have a number of important implications. First, the modest magnitude of the stimulatory response makes hormesis difficult to prove. This has been a reason for its slow acceptance by the scientific community. The assessment of hormesis-related hypotheses requires the use of more subjects to enhance statistical power calculations because the expected response is modest and control group variation, depending on the biological model, can be an important concern; more doses are also often needed to carefully define the nature of the dose response in the low-dose (i.e., below threshold) zone; multiple temporal evaluations (i.e., repeat sampling activities) are needed to detect the compensatory response [38]; there is also an enhanced need for replication given the modest nature of the low-dose stimulatory effect. Efforts to increase statistical power and to ensure that the results are consistently reproducible are necessary in order to determine whether the hormetic stimulation is “real” and not accounted for by normal background variation. Many investigators are reluctant to design and conduct such rigorous investigations due to the extra time and resources required. This has resulted in dose–response relationships being inadequately designed, especially in the low-dose zone where the greater resources need to be directed.

Investigators often justify the use of only a few high doses since the threshold model assumes that there are no treatment-related effects below the threshold. These assumptions and the practices that gave birth to the threshold model are what resulted in toxicology evolving into a few high-doses discipline, a practice that has led many to question its capacity to offer insights on the critical questions of today that deal with a preponderance of low-dose exposures to complex mixtures.

A second implication of the modest stimulation is that it relates principally to biological performance, not toxicity. The hormetic dose response indicates that chemicals/drugs that induce a low-dose stimulation will be constrained by the

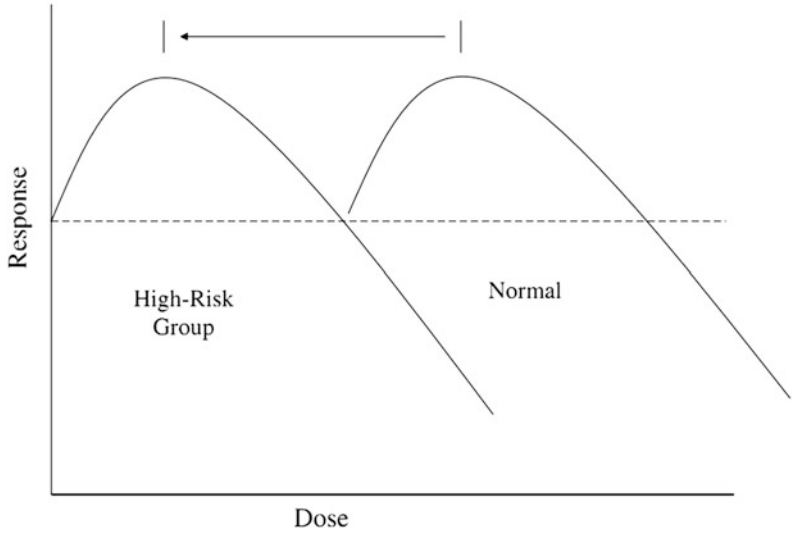

Fig. 2 Stylized dose–response curves illustrating the presence of a hormetic response in high-risk groups. This response occurs at lower doses compared with the response in the normal population and thus the dose–response curve for the high-risk group is shifted to the left of the dose–response curve for the normal population

quantitative features of this dose response [39]. For example, agents that increase cognition, hair growth, longevity, and other performance endpoints are constrained to do so within the 30–60% range of the hormetic dose response. This is the case even when two or more drugs interact in an additive or synergistic fashion [40, 41]. In effect, the concept of synergy in hormesis is far different from that seen in traditional toxicology [42]. In toxicology, the focus is on the magnitude of the response (i.e., toxicity). In hormesis, it is principally on the dose, with the response maxima being constrained. In addition, the hormetic dose–response constraints are seen even when chemicals have profoundly differing potencies. That is, two agents that differ by over a millionfold in toxic potency will nonetheless display the same quantitative features of their respective hormetic responses. The only difference is that the more potent agent will have its dose response shifted far to the left.

The width of the hormetic dose response and its relationship to the toxic threshold are also important factors to consider. The hormetic stimulation is generally fairly close to the toxic threshold, with the maximum hormetic stimulation being within about a factor of 5–10 of the threshold. This has important implications, especially for heterogeneous populations such as with most human groups. Since human interindividual variation can exceed a factor of one hundred [43], it would not be unexpected that what may be a beneficial hormetic response for some may be in the toxic zone for others (Fig. 2). Since target doses are not based on genetic individuality but typically determined by body weight or surface area [44], it is likely that drugs whose beneficial response is in the hormetic zone could have the potential to induce toxicity in the high-risk segments of that

population. On the other hand, if there were a broad hormetic stimulatory zone, the clinician could target the drug dose optima to be further from the toxic zone with the patient still receiving the intended beneficial effects [45].

Hormesis: An Adaptive Response

The hormetic stimulation has been observed to represent an overcompensation to a disruption in homeostasis [46–48]. The hormesis phenomenon is therefore a dose-time response in which there is an initial stress or damage induced by the causative agent. However, the affected biological system responds in a compensatory manner to repair the damage. The compensatory response usually slightly overshoots the original homeostatic set point (i.e., equal to the control group value). This is reflected in the modest stimulation that characterizes the hormetic response in the low-dose region. However, at high doses where toxicity is excessive, a full and successful compensatory response is usually not achieved, and this is reflected in the high-dose toxicity response. The hormetic stimulation response therefore is adaptive in nature and represents a reparative response of the affected biological system. The response to the low-dose induction of damage also affects a series of prosurvival adaptive responses that permits the biological system to be protected against a more massive subsequent exposure to the toxic agent. This has been referred to as an adaptive or conditioning response. This dose response of the "adapting" or the "conditioning" doses to the more massive subsequent treatment follows the inverted U-shape of the hormetic dose response [49].

While hormesis is generally viewed as an adaptive response, there are situations when it can be considered maladaptive. For example, low doses of many antitumor agents can enhance the proliferation on tumor cells. This has now been recognized and under certain circumstances may pose an enhanced risk to the patient [50]. This same type of process could also occur following exposures to antibiotics, antifungal agents, and antiviral medications. It is possible that the low-dose stimulation could be harmful if it enhanced endpoints related to autoimmunity [51]. Likewise, certain drugs, such as ouabain, that have been used to treat congestive heart failure can enhance the proliferation of smooth muscle of the prostate gland by about 30% [52]. This magnitude of enlargement may be sufficient to cause clinical symptoms in affected patients. Thus, the concept of benefit and harm should be decoupled from the definition of hormesis [53] since the implications of the low-dose stimulation could be beneficial, harmful, neutral, or unknown.

Hormesis: An Example of Biological Leveraging

While recognizing the potential adverse effects of the low-dose stimulation and how these may be dealt with in order to enhance healthy outcomes, it is important to

place the hormetic dose responses in a broad context. The hormetic dose response is an adaptive strategy that reflects a type of "biological leveraging." The low-dose exposure induces a stress or low-grade toxicity response. The affected biological system then generates a compensatory response that typically exceeds the original set point condition (i.e., equivalent of the control response) in a modest fashion (i.e., 30–60% at maximum). This response not only repairs the initial modest damage but also provides benefits that significantly outweigh the costs of the initial investment (i.e., the initial stress or toxicity). Hormesis may therefore be seen as an investment strategy that not only protects against status quo stresses (i.e., the induced modest toxicity and background toxicity by about 30%) but also preadapts the affected system(s) against potential catastrophic loss, that is, death or significant disability. The concept of biological leveraging is seen in numerous toxicological and biomedical settings (e.g., adaptive responses to radiation and chemical mutations; preconditioning hypoxic stress and its protection against cardiac injury) [49, 54]. All such situations have an adapting dose or conditioning stress optima which conform to the quantitative features of the hormetic dose response.

Hormesis and Drug Discovery/Development

The hormetic dose response is also being exploited routinely in the pharmaceutical world but usually under the guise of terms such as biphasic, U-shaped, and bell-shaped, that is, interchangeable terms for the same dose–response relationship. For example, detailed evaluations within the field of antianxiety drugs revealed that essentially all the standard animal screening tests (e.g., elevated plus maze, hole board test, light–dark test, four plates test, open field test, staircase test, social interaction test) demonstrate inverted U-shaped dose responses, all consistent with the quantitative features of the hormetic dose response [55]. In such cases, the low-dose stimulation typically reflects the zone of reduced anxiety. Thus, in these instances, the hormetic dose response is that which is used to screen and judge antianxiety drugs and move the effective ones along for further testing.

With respect to antiseizure drugs, animals are employed to assess agents that can modulate chemically induced seizure thresholds. Those agents that can increase the chemically induced threshold dose, that is, making it harder to induce a seizure, may have potential as antiseizure agents. In this case as well, effective antiseizure agents act biphasically in a manner consistent with the hormetic dose response, increasing the threshold at low doses while decreasing the threshold (i.e., making it easier to induce a seizure) at higher doses. This is another case where pharmaceutical companies have long been using the hormetic dose–response concept [56]. In the case of memory and cognitive dysfunction, including those approved for the treatment of Alzheimer's disease [57], all have shown the typical inverted-U of the hormetic dose response, again with the same quantitative features of the dose response. Similar effects have been reported for pain modulation [58], for chemical-induced nausea [58], for protecting neurons from a wide range of

chemical-induced stressors [59], for enhancing neuronal outgrowths [60], for experimentally induced stroke damage/brain traumatic injury [61], and for drug addiction [62].

The neurosciences therefore display a broad and extensive array of hormetic dose responses. Until very recently, the term hormesis only rarely has been used to describe the plethora of hormetic dose responses in this area [54]. The field has typically used nonspecific terms such as biphasic, dual effects, U-shaped, bell-shaped, pharmacological inversion, nonmonotonic, and others for hormetic-like dose–response relationships. However, these various dose responses share the same quantitative features and the same inherent constraints. In effect, this seemingly highly diverse array of biphasic dose–response relationships is all hormetic. This is the case for other biomedical domains, as has been recently shown for immunological responses [50], human tumor cell responses [51], and the vast array of other areas reflected in the hormesis database [27].

Hormesis: Gaining Visibility and Acceptance

It is important to note that the hormetic dose response is being rediscovered by the scientific community or, to be more accurate, discovered for the first time. For example, leading textbooks in human and environmental toxicology now include sections on hormesis [21, 63–65]; entire chapters have been published in textbooks dealing with aquatic toxicity [39] and pharmacology [22], and chapters have been included in a number of monographs [47]. Within the year 2010, three books have been published on hormesis [66–68]. Major professional societies, such as the US Society of Toxicology (SOT), have recently had a major session on hormesis at their annual conference. Even more notable is that leading indexing services such as the Web of Science reveal over 1,500 citations on hormesis, with more than 80% of those since 2000. Despite this positive indicator of growing interest, this number may substantially underestimate/hormetic dose responses, due to the use of alternative terms, among other factors. Hormesis has also been the object of numerous detailed stories reaching the general public as seen in substantial articles in *The Wall Street Journal* [69], *U.S. News & World Report* [70], *Discover Magazine* [71], *The Boston Globe* [72], *The Baltimore Sun* [73], *Science News* [74], as well as a four-page detailed story in the news section of *Science* [75].

Summary

The hormesis story is important for a number of reasons. First, it has revealed that the historical foundations leading to the acceptance of the threshold dose–response model throughout the twentieth century and even down to today were based on political and economic concerns rather than science. This analysis also reveals what

may be hard to believe and even more difficult to accept. That the field of toxicology and the biomedical sciences in general accepted the threshold dose–response model without validation of its capacity to predict responses in the low-dose zone (i.e., below the toxic/pharmacological threshold) and then continued to apply this unproven model for that purpose for at least the past six decades, jeopardizing the public health while thinking it was doing what was scientifically correct. That an entire field could make a mistake on the central pillar of its discipline and perpetuate that error for generations of scientists is as remarkable as it is disconcerting. Despite the historical blunders that have guided toxicology and regulatory agencies on the nature of the dose response, the hormesis story provides a key framework for guiding the scientific community in the development of a new generation of pharmaceutical agents and chemically based products that can better exploit the nature of the dose response to enhance human and environmental health, respectively, including more protective and scientifically based health standards, to enhance biological efficiencies in a broad range of systems of economic and health benefit, to improve cost-benefit assessments, and to better understand the limitations of biological systems due to plasticity restrictions in the development of pharmaceuticals. Hormesis can provide insight in addictive behaviors as self-administration of addictive drugs often follows the quantitative features of the hormetic dose response [60]. Finally, the emerging evidence indicates that there is a healthy side of stress that can and should be exploited for personal and societal gain. However, the dose response must be both better understood and respected because by its very nature it is biphasic, and these phases can be in close proximity, with health and disease being close neighbors.

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