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REVIEW ARTICLE

What is hormesis and its relevance to healthy aging and longevity?

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Abstract This paper provides a broad overview of hormesis, a specific type of biphasic dose response, its historical and scientific foundations as well as its biomedical applications, especially with respect to aging. Hormesis is a fundamental component of adaptability, neutralizing many endogenous and environmental challenges by toxic agents, thereby enhancing survival. Hormesis is highly conserved, broadly generalizable, and pleiotrophic, being independent of biological model, endpoint measured, inducing agent, level of biological organization and mechanism. The low dose stimulatory hormetic response has specific characteristics which defines both the quantitative features of biological plasticity and the potential for maximum biological performance, thereby estimating the limits to which numerous medical and pharmacological interventions may affect humans. The substantial degrading of some hormetic processes in the aged may profoundly reduce the capacity to respond effectively to numerous environmental/ischemic and other stressors leading to compromised health, disease and, ultimately, defining the bounds of longevity.

Keywords Hormesis · Biphasic · Adaptive response · Preconditioning · Aging · Dose–response

Introduction

Over the past several decades there has been a substantial increase in the reporting of hormetic dose response relationships and their assessment in the biological and biomedical literature. In the decade of

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the 1980s the terms hormesis or hormetic were cited about ten times per year in the Web of Science database; in 2013 and 2014 alone these terms were cited over 6000 times, a greater than 600-fold yearly increase. This increase is widespread affecting a broad range of biological and biomedical areas. There have been eight recent books on hormesis from various perspectives (Costantini 2014; Elliott 2011; Krenz et al. 2013; Le Bourg and Rattan 2009; Mattson and Calabrese 2010; Rattan and Le Bourg 2014; Saunders 2010; Stebbing 2011), reflecting the broad range of its interest and implications. Likewise, hormesis has been a focus of numerous conference symposia within established professional scientific societies (e.g., Society of Toxicology, Society for Risk Analysis, American Chemical Society, Health Physics Society, American Nuclear Society, and others), and the focus of several recent journal special issues (e.g. Journal of Cell Communication of Signaling-2014; Homeopathy-2015) and the foundation of a government funded Ph.D. training program in Germany (i.e. Friedrich-Schiller University—Jena) on hormetic molecular mechanisms. Hormesis has also received widespread discussion in more general publications (Ahuja 2003; Bailey 2003; Begley 2003; Bell 2004; Boyce 2004; Cook 2003; Hively 2003; Lambert 2003; Pike 2004; Raloff 2007; Renner 2003; Roberts 2003; Stipp 2003) and in leading scientific journals (Calabrese and Baldwin 2003a, b; Kaiser 2003).

While this reawakening of intense interest in hormesis is a recent phenomenon, renewed interest began to emerge about 40 years ago with the publications of Donald Luckey concerning ionizing radiation (Luckey 1980, 1991), Anthony Stebbing concerning marine toxicology (Stebbing 1976, 1982, 1987, 1998) and Elmer Szabadi (Szabadi 1977) concerning pharmacology. These notable independent developments were followed by researchers in other fields (e.g., immunology, epidemiology, cancer research, plant science, wound healing) who reported the widespread occurrence of hormetic-like biphasic or U-shaped dose responses. However, unlike the false starts of earlier decades, the intellectual and scientific convergence of hormetic findings have been sustained and significantly expanded over the past several decades. It is thus timely to consider the relevance of hormesis for aging research, including what hormesis is, why this concept was essentially unknown only several decades ago, why it is receiving considerable interdisciplinary attention, what may be its biological significance and potential applications, and how it may affect the future of aging research.

Hormesis in historical perspective

The term hormesis, from the Greek meaning to excite, was first employed in the scientific literature in 1943 by Southam and Erhlich (1943) based on their extensive findings with fungal responses to various plant extracts. The term hormesis would eventually come to replace several earlier descriptors such as the Arndt-Schulz Law or Hueppe's Rule (Calabrese 2005a). Hormesis is a biphasic dose response that is characterized by a low dose stimulation and a high dose inhibition (Calabrese 2010; Calabrese and Baldwin 2002). As such it is a type of biphasic dose response, but one with specific quantitative features with respect to its amplitude and width and its relationship to the onset of the threshold response or zero equivalent point/dose for toxic and pharmacological effects (Fig. 1). This dose response was not only widely ignored by the scientific and medical communities for the entire twentieth century, but often the object of ridicule (Calabrese 2011, 2004). Despite its widespread reporting in the scientific literature by numerous highly regarded investigators during the first half of the past century (Calabrese and Baldwin 2000a, b, c, d, e), it was omitted from all leading textbooks of pharmacology and toxicology during this period and for the remainder of that century, never included as a topic at symposia of major professional societies and ignored by national regulatory agencies in the framing and execution of public health policies and regulations for the assessment of ionizing radiation, drugs and chemicals and not included for research funding by federal and international governmental agencies (Calabrese 2005b).

The hormesis concept formally originated with the research of the German pharmacologist Hugo Schulz in the early to mid-1880s (Schulz 1887, 1888). In this research Schulz sought an alternative chemical disinfectant for carbolic acid, which had been used by Joseph Lister with great success for aseptic surgery. However, carbolic acid had a range of unattractive features, thereby generating Schulz's interest in alternatives. In a series of experiments he evaluated nearly a dozen agents on yeast. While he was expecting all the agents to kill the yeast in a dose dependent manner,

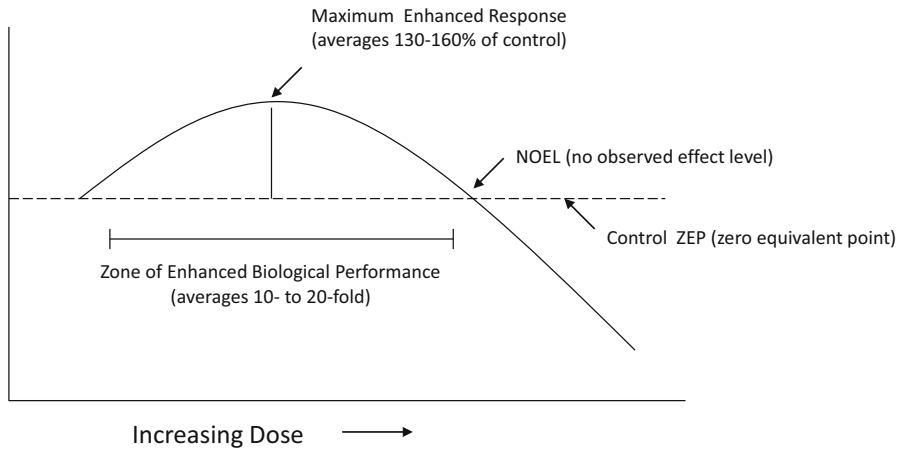

Fig. 1 Dose response curve depicting the quantitative features of hormesis and its application to the concept of enhanced biological performance

Schulz became surprised when experiments consistently revealed enhanced metabolism at low concentrations while being inhibitory at the higher concentrations. Schulz thought that he had introduced a methodological error into the experiments but repeated testing confirmed the reproducibility and legitimacy of his initial observations (Crump 2003). These findings should have been of considerable potential value to people such as Lister as they broadened the domain of disinfectant options. However, Schulz failed to emphasize this point, while claiming that his findings provided the explanatory principle of the controversial medical practice of homeopathy, unleashing a storm of criticism and skepticism within the traditional medical and academic communities profoundly subduing what should have been considerable biomedical interest in the implications of his findings (Bohme 1986).

The "explanatory principle" claim of Schulz was based on his linking of several disparate findings into a unified dose response concept. First, Schulz was aware that the homeopathic agent veratrine was reported to effectively treat gastroenteritis (Bloedau 1884). Second, Schulz was not successful in showing that veratrine could kill or inhibit the growth of the bacterium that caused this disease regardless of the dose (Bohme 1986). Nonetheless, he still believed that the veratrine treatment was successful but it was not due to killing the disease causing organism but via an alternative mechanism. Third, Schulz linked these observations with veratrine to his low dose yeast data and asserted that the veratrine most likely affected a cure via the induction of adaptive processes at low dose. Fourth, he then generalized this perspective to other homeopathic drugs and many pharmaceutical agents.

Schulz and his work were soon marginalized by his colleagues within the medical and academic communities who were engaged in a long term and intense conflict with the homeopathic movement. By siding with the opponents of what we may today call traditional medicine, Schulz quickly became professionally ostracized and would have his career profoundly marginalized (Wels 1933). The conflict would continue his entire professional life as he was the object of long term criticism (Clark 1933, 1937). Despite the fact that Schulz promoted the biphasic dose response he placed this concept in serious peril since his opponents were organized and often outstanding leaders, including some of the most accomplished and broadly influential researchers in pharmacology and toxicology. The net result was the marginalizing and trivializing of the biphasic dose response within the scientific and biomedical communities. Thus, almost before he started, the career of Schulz and his dose response theory were significantly curtailed.

There were many highly regarded investigators during the five decade professional lifetime of Schulz who observed biphasic dose response relationships in their experimental research (Calabrese 2009a, b). However, their published findings were never well integrated within a broad multi-disciplinary scientific framework. In general, they failed to organize,

develop a focus, and appreciate the quantitative features of hormetic responses or study design features needed to adequately assess them. Lacking adequate leadership and a scientific framework, the hormesis concept failed to mature, especially in the face of unrelenting opposition, especially by leaders in pharmacology such as Alfred J. Clark (1933, 1937) who's influential writings helped to ensure that Schulz's "explanatory principle" of homeopathy (i.e., the biphasic dose response) would not be accepted. It should be noted that Schulz did not accept the high dilutionist philosophy of Hahnemann but rather a "low" dilution framework for homeopathy, with readily quantifiable molecules in homeopathic treatments (Bohme 1986). Nonetheless, inaccurate and unfair criticism by Clark (1933, 1937) resulted in Schulz being seen as a follower of Hahnemann's high dilutionist views, a criticism that would not only strongly taint his career, but also strongly marginalize his biphasic dose–response theory.

While the medical community was strongly opposed to the homeopathically-associated biphasic dose response of Schulz, it needed a dose response of its own. Since it could not adopt the dose response model of its opponent, it eventually settled on the threshold dose response which had considerable support in the literature (Clark 1933, 1937; Shackell 1923, 1925; Shackell et al. 1924/1925) and was consistent with broad personal experience. Thus, the choice was easy. The adoption of the threshold dose response model by the medical community became progressively accepted and carried over to the regulatory community. The threshold dose response would eventually become the default model for essentially all regulatory actions (Lehman and Fitzhugh 1953).

The twentieth century was, therefore, one in which acceptance of the biphasic dose response was linked early on to the fate and status of homeopathy. With the demise of homeopathy during the early decades of that century (Coulter 1972, 1982), the biphasic dose response experienced a similar fate, principally due to the strategic mistake of Schulz starting in the 1880s and its continuance well into the next century.

Hormesis: the modern era

While the twentieth century would witness numerous publications concerning biphasic dose responses, such findings were not widely appreciated and failed to influence key scientific leaders, developments and judgements. This would begin to change as the twentieth century was drawing to a close due, in part, to the fact that the U.S. environmental/public health regulatory agencies had adopted the highly conservative linear dose response model for cancer risk assessment, being guided by a strong precautionary principle. The use of the linear dose response model imposed very high costs upon regulated industries that tried to challenge government regulatory decisions based upon it. A common industry strategic plan was simple enough: convince regulatory agencies to soften the highly conservative approach, reverting back to the threshold dose response model. However, such efforts failed as most toxicological studies lack sufficient doses to adequately distinguish, in a statistical manner, between linear and threshold dose response models in the low dose zone. As a result, the regulatory agencies would invariably default to the more conservative (i.e., protective) linear model. After numerous failed challenges to regulatory agency risk-based decisions, many industrial associations recognized that this debate was futile. As a result of their stymied position, the regulated industry, especially the nuclear industry, became intrigued with an alternative dose response perspective offered by University of Missouri Professor Thomas Luckey (1980) in his book, Ionizing Radiation and Hormesis. Although not fully persuasive, the Luckey (1980) book was important as it provided copious and detailed documentation of hormetic dose responses, arguing that it was more valid than linear or threshold models. Five years earlier the intuitive Luckey (1975) recommended that regulatory agencies consider the hormesis concept in the emerging domain of environmental human risk assessment. However, this suggestion was never heeded nor formally considered.

Luckey (1980) provided a key stimulus for the electric power industries of Japan and the U.S. to conduct the first conference on hormesis in August 1985 in Oakland, California, with proceedings published 2 years later in the journal Health Physics. The meeting would give new visibility to the hormesis concept and stimulate others to reconsider the nature of the dose response in the low dose zone, raising the question of whether hormesis was a real, reproducible phenomenon and, if valid, what were its implications for medicine and environmental risk assessment. By the late 1980s multiple factors were converging that

would propel the assessment of hormesis forward (Sagan 1989; Wolff 1989). Along with the growing dissatisfaction with the regulation of carcinogens, these included the integration of basic scientific discoveries (e.g., DNA repair, apoptosis, adaptive response/preconditioning, immune defense mechanisms, epigenetic cancer mechanisms) that could affect the shape of the dose response in the low dose zone. Furthermore, there was also growing recognition that high dose damage mechanisms, as may occur in the standard chronic cancer bioassay, were not appropriate for estimating low dose cancer risks (Ames 1987; Ames et al. 1987; Ames and Gold 1990).

The hormetic challenge

These efforts led to a series of integrated activities to explore the concept of hormesis involving annual interdisciplinary conferences, the creation of an hormetic dose response data base using a priori evaluative criteria (Calabrese and Blain 2005, 2009, 2011) and other more specialized hormesis data bases (Calabrese and Baldwin 2003b; Calabrese et al. 2006, 2008, 2010) to estimate the frequency of hormesis and assess other scientific questions.

The creation of the various databases provided a robust volume of studies demonstrating hormetic dose responses that were compliant with rigorous evaluative criteria. This permitted reliable evaluations of the quantitative features of the hormetic dose response, as well as its generality across a broad range of biological models, ranging from plants to microorganisms to invertebrate and vertebrate models. The databases also permitted the assessment of hormesis across different levels of biological organization, ranging from the cell to the organ to the organism. These collective assessments revealed that hormesis was highly generalizable, being independent of biological model, level of biological organization, inducing agent and mechanism. Furthermore, the hormetic dose response also was unexpectedly shown to have specific quantitative features, with the amplitude of the low dose stimulatory response being modest, with about 80 % of the dose responses in the hormetic data base having a maximum response less than twice the control group, with most of these only 30–60 % greater than the control at the maximum response. The width of the stimulatory dose response was more variable but typically in the 5–20-fold zone starting immediately below the zero equivalent point or threshold dose. For about 5 % of the database the width of the stimulatory response range exceeded 1000 fold in reproducible assays (Calabrese and Blain 2005, 2009, 2011).

Of considerable importance was that a specialized database using rigorous a priori entry and evaluative criteria provided an estimate of the frequency of hormesis within the biomedical and toxicological literature. The estimated frequency approached 40 % and far exceeded that of other commonly employed models. For example, the hormetic dose response was shown to occur approximately 2.5-fold more often than the threshold model which itself was more common than a linear model (Calabrese and Baldwin 2003b). When tested with several other large data sets the threshold model performed poorly in each case while the opposite was true for hormesis (Calabrese et al. 2006, 2008, 2010). Thus, it seemed clear that the threshold model might be very limited and seriously flawed while the long neglected and marginalized hormetic model was a consistently strong performer.

These striking findings lead to the question of whether and how the scientific and regulatory communities had validated the threshold model as it was the foundation for substantial regulatory activities in many countries throughout the twentieth century. However, a prolonged and detailed investigation of this question failed to reveal that any organization or person ever attempted to validate the threshold model prior to our above cited direct head-to-head comparisons. Thus, it appears that the adoption of the threshold dose response model was made without ever having been validated for low dose responses, the zone where humans principally reside.

Features of the hormetic dose response

The hormetic dose response occurs via the induction of a direct stimulatory response or as a result of a modest overcompensation to an initial disruption in homeostasis (Calabrese 1999, 2001; Calabrese and Baldwin 2001a). In this later case, the hormesis dose response would require a time component in order to be detected and studied. The quantitative features of such dose responses were similar whether the response occurred via a direct stimulation or via an overcompensation response. This revealed that the quantitative features of hormesis was independent of mode of action. This convergence of observations suggested an answer to

why hormetic effects were modest, often difficult to observe. Overcompensation stimulation appeared to be an evolutionary adaptation to disruptions in homeostasis to ensure that mild toxicities could be rapidly repaired/reversed with little waste of limited biological resources.[1] Thus, it would make little sense for a compensatory system to overshoot its set point goal by orders of magnitude. Furthermore, the modest stress not only led to an overcompensation recovery but also provided protection against a subsequent more massive and even life threatening challenge, which is now referred to as a preconditioning response (Calabrese 2007; Calabrese et al. 2007). The preconditioning response also displays a hormetic-biphasic dose response, further generalizing this dose–response concept within an optimization framework.

Further extension of the hormesis/preconditioning phenomenon to other experimental modalities has been reported. That is, an hormetic response may also occur via treatment of a biological system that has been seriously damaged by a prior massive exposure such as a heart attack or stroke (Krenz et al. 2013). This therapeutically beneficial treatment has been designated as post-conditioning. The hormetic dose response may, therefore, be elicited via multiple experimental protocols based upon direct stimulation and overcompensation stimulation following a disruption in homeostasis, which can incorporate both pre- and post-conditioning contexts. Furthermore, the quantitative features of these dose responses in each experimental context are similar. How could the quantitative features of the hormetic dose response be similar regardless of the biological model, endpoint measured, inducing agent, level of biological organization (cell, organ, organism), and mechanism?

The extensive generality of the hormetic response and its dose–response constraints suggest that it provides a reliable quantitative estimation of the limits of biological plasticity with a description how much gain is in the system. The assessment of hormesis indicates that the limits of plasticity is evolutionarily-based, highly conserved, common across all phyla, as well as being allometrically-based, being a function of body weight and/or body surface area (Calabrese 2013a; Calabrese and Mattson 2011). This suggests that the hormetic concept may be viewed as a biological blueprint or architectural design trait whose functions may be mediated by an allometric gene cluster that orchestrates structure/functional control patterns, at all levels of biological organization (Bernstein 2010). Such generic, multi-tiered, and integrated biological organizational mechanistic regulation provides a theoretical framework for placing the hormetic concept within a broad biological context.

While the above discussion focused on why the quantitative features of the hormetic dose response are modest and highly generalizable, large numbers of specific/proximate mechanisms have been reported that mediate hormetic dose responses. In 2013, 400 examples of specific hormetic mechanisms were published in which the hormetic stimulation was mediated via a specific receptor and/or cell signaling pathway (Calabrese 2013b). Thus, despite a plethora of specific mechanisms in multiple systems and experimental contexts, the quantitative features of the dose responses were similar.

These general and quantitative features of hormesis have profound biological implications since they describe and determine the limits to which integrative responses in biological systems can be enhanced. Such hormetic control features are reported for an extremely broad range of biological processes that depend upon dose/concentration gradients. For example, during developmental periods the hormetic dose/concentration gradient may affect the creation of biological curvatures such as with the shape of the eye, capillaries, the head of the femur, etc. (Fosslien 2002, 2009). Such curvatures may occur due to concentration gradients (Calabrese and Baldwin 2001b) that stimulate cell proliferation via multiple growth factors at low concentrations while being inhibitory at higher concentrations, much like how an airplane obtains lift. This provides a means to enhance rapid growth on one side of a cellular plane as compared to the other side which is inhibited by the higher concentrations. The net result would be the formation of curvature-like growth. Such a process could result in the growth around a lumen, with the formation of a capillary structure principally due a hormetic-biphasic concentration relationship.

[1] More recently, the term "hormetin" has been introduced to describe an agent that can induce some molecular damage, which then induces cellular stress responses as a defense mechanism (Demirovic and Rattan 2011; Rattan 2012). This definition is derived from the overcompensation stimulation feature of the hormetic dose response.

Hormetic-like biphasic dose responses are also the means by which numerous receptor systems work (Calabrese 2001, a, b, c, d, e, f, g, h). Such systems affect essential functions in most, if not all, cell types. Thus, a central biological strategy that has been largely preserved from bacteria to humans is the use of ligand concentration gradients that mediate how cells, organs and organisms develop, grow, maintain themselves, migrate, reproduce, repair and defend.

The hormetic concept also affects the search for new pharmaceuticals (Calabrese 2008a) with most anxiolytic (Calabrese 2008b), anti-seizure (Calabrese 2008c), and memory drugs (Calabrese 2008d) displaying hormetic/biphasic responses (Calabrese 2008e). This has important implications such that drugs that are intended to improve biological performance (e.g., grow hair, accelerate wound healing, strengthen bones) are stimulated at most only by about 30–60 %, the plasticity constraint described by the hormetic dose response. Such enhancements can be readily observed in microbe, plant and animal models under controlled experimental conditions. This can be more difficult to demonstrate in the case of human testing where there is considerable interindividual variation in genetic background, health status, dietary practices and other factors. This presents important challenges in the efficacy testing of performance enhancing drugs in people.

Hormesis and aging

Lifespan

Hormesis has long been shown to affect an increase in the lifespan. Davey (1917) reported that low doses of ionizing radiation increased the lifespan of the Confused Beetle (*Tribulium confusion*). The investigations of Davey (1917, 1919) were remarkable for the era, incorporating key concepts of study reproducibility, sample size, confounding variables, dose range, and spacing and number of doses as well as statistical analysis. The findings of Davey (1917, 1919) were replicated by Cork (1957) using the same biological model but a gamma ray source, rather than X-rays. Similar enhancements of lifespan with various insect models by ionizing radiation have now been widely reported, showing strong consistency with the hormetic dose response (Calabrese 2012, 2013c).

The basic concept of Davey that a low dose of a stressor agent might prolong lifespan has been extended by numerous investigators using chemical agents and various forms of ionizing radiation in multiple biological models, such as nematodes (Cypser and Johnson 2002; Olsen et al. 2006; Ristow and Schmeisser 2011), insects (Le Bourg 2011; Sarup and Loeschcke 2011), and mammalian models (Calabrese and Baldwin 2000f; Kahn and Olsen 2010; Marques et al. 2010; Pardon 2010; Salminen and Kaarniranta 2010). Extensive experimental research by Kitani et al. (2002, 2005) indicated that antioxidant enzyme activity was closely associated with the capacity of deprenyl to enhance longevity at low doses, displaying an hormetic effect. The convergence of these and many other consistent observations led Hunt et al. (2011) to suggest that these multiple ways of increasing lifespan support the hypothesis that functioning stress response pathways merge or converge with prolongevity pathways. Such inter-relationships between stress and aging further support the premise that activation of specifically targeted hormetic mechanisms may prolong life and/or retard the occurrence of age-related functional impairments. These findings generally reflect the capacity to increase life span within the quantitative constraints seen with the hormetic dose response.

Aging and preconditioning

Preconditioning has become a prominent area of research in the biomedical domain, with particular focus on cardiovascular and brain diseases although substantial research has been extended to kidney, lung, liver, skin and stem cells. Preconditioning is a phenomenon in which a prior stress affords protection against a subsequent and more severe challenging exposure/dose. While this was first shown to occur within the context of ischemic preconditioning providing substantial protection from damage due to a massive myocardial infarction in dogs (Murry et al. 1986), these findings were quickly replicated and generalized to other organs and animal models. Since the reporting of preconditioning by Murry et al. (1986) there have been over 5000 studies in mammalian models which have confirmed and extended this concept and its potential applications. The preconditioning methodology has been extended to include a

post-conditioning aspect in which the conditioning treatment is administered during and/or after the reperfusion phase of the challenging dose. Furthermore, both pre-and post-conditioning can be induced remotely (i.e., at a site other than the tissue and organ of interest) as well as pharmacologically (Heusch et al. 2015).

Even though preconditioning can affect a clinically significant protective multi-organ adaptive response, considerable evidence indicates that its effects can be significantly diminished in aged animals in experimental settings and in elderly humans (>65 years). This age-related ischemic preconditioning adaptive response reduction was first reported by Abete et al. (1996) using an isolated and perfused heart model with benefits seen in 4 month old rats being lost in 24 month old rats. This seminal observation paved the way for numerous follow up studies showing a comparable age-related loss of preconditioning induced heart benefits in mice (Boengler et al. 2007), rats (Ebrahim et al. 2007; Fenton et al. 2000; Lu et al. 2001; O'Brien and Howlett 2008; Schulman et al. 2001; Tani et al. 1997), rabbits (McCully et al. 1998), and humans (Abete et al. 1997; Bartling et al. 2003; Ishihara et al. 2001; Lee et al. 2002; Longobardi et al. 2000; Napoli et al. 1999). While the mechanisms affecting such reductions in preconditioning performance in the aged animal/elderly human remains to be clarified, it appears to be related, at least in part, to a decrease of norepinephrine release via α_1-adrenoreceptor stimulation following ischemic preconditioning (Abete et al. 2010). Despite the collective consistency and strength of such observations on age and related reductions in the preconditioning responses, others have not reported similar losses of protective effects in aged rats (Yin et al. 2009), sheep (Burns et al. 1996), and humans (Loubani et al. 2003), highlighting the importance of further examination of the complex interactions between aging and the preconditioning phenomenon.

According to Krenz et al. (2013) the mechanisms underlying the effect of aging to diminish the capacity of preconditioning to protect the heart and other organs may be due to impaired activation of signaling. They suggested that this may be overcome, at least in part, by increasing the amplitude of the triggering stimulus, by increasing the duration or number of bouts of preconditioning ischemia/reperfusion as well as by the overexpression of pathway receptors such as adenosine A1 receptors. In a complementary approach, several studies reported partial restorations of age-related hormetic preconditioning protective responses following some types of exercise training (Abete et al. 2000; Kwak et al. 2006; Masoro 1998; Powers et al. 2004) and caloric restriction procedures (Abete et al. 2002a, b; Jahangir et al. 2007; Long et al. 2002; Pepe 2001; Rohrbach et al. 2014).

Although studied to a more limited degree, similar age-related decrements in the protective effect are seen in the brains of animals. For example, the protective effects of ischemic preconditioning against global cerebral ischemia was reduced in 24 month old as compared to 4 month old rats (He et al. 2015, 2006). While more limited studies have exploited the capacity for preconditioning methods (e.g., caloric restriction, physical activity, etc.) to affect neuroprotection than with the cardiovascular domain, the trend is similar with exercise (Barrientos et al. 2011; Chrysostomou et al. 2014; Garcia-Mesa et al. 2014; Park 2010), caloric restriction/intermittent fasting (Newton et al. 2008; Tesic et al. 2015; Vasconcelos et al. 2015) and remote preconditioning (Meng et al. 2015) which show significant restoration of function in aged subjects. For example, caloric restriction increases brain–derived neurotrophic factor (BDNF) in key brain regions such as the CA1 (Newton et al. 2008), in a manner similar to the age-related increase in BDNF in the DG and CA3 regions, suggesting that it may enhance adaptive mechanisms that typically occur during aging to ensure proper maintenance of homeostasis.

Other studies have reported that hypoxia preconditioning of bone marrow cells from aged mice (20–22 months of age) was effective in enhancing angiogenic potential, with little decline with age (Kubo et al. 2012). These results were sufficiently encouraging to further efforts to explore the therapeutic effectiveness of cell-based angiogenesis in clinical trials. The mixed results of preconditioning in aged animals and elderly humans represents a significant challenge and opportunity.

Adaptive response to ionizing radiation: aging effects

The adaptive response to ionizing radiation induced damage is also affected by the aging process. For

example, in 1998 Gadhia (1998) first reported that the adaptive response may be age dependent for X-ray induced damage in human lymphocytes. In this study, adaptive response was evident over ages ranging from 5 to 45 years, with a typical decrease in mutation rate of 60–80 %. However, in those aged $\geq$65 years, the protection was not apparent. Such findings were expanded by Miura et al. (2002) to glial cells in Wistar rats when the radiation adaptive response was evident at 1 month of age but lost by 24 months. Similar findings with differing inducing agents and a broad range of conditioning doses on glial cells supported the initial findings (Miura 2004; Miura and Endo 2010; Calabrese 2008f). These age dependent findings are consistent with those reported for preconditioning in the biomedical sciences for age-related decrements.

Discussion

Hormesis is a highly conserved general dose response strategy providing the means by which numerous cell types, probably all organs and whole organisms carry out development, growth, maintenance and repair processes via a vast array of receptor based signaling and other mechanisms (Table 1) (Calabrese 2008f). It is also an adaptive dose response strategy that anticipates potential threats as seen with preconditioning but also can prevent damage even after potentially harmful exposures as seen within a post-conditioning framework (Calabrese et al. 2007; Roberge et al. 2008). Of critical importance is that these dose response survival enhancing activities are achieved via a manifestation of the parsimony principle in which a tightly integrated and managed system ensures that biological resources are carefully allocated and conserved as seen in the modest quantitative stimulatory features of the hormetic dose response. The redundant flexibility of the hormetic dose response is manifest via its direct stimulation or rebound/overcompensation response to a disruption in homeostasis. Regardless of the activating process, the quantitative features of their dose responses are similar. In addition to its generality across experimental models and levels of biological organization, the hormetic dose response is also independent of the endpoint measured, the inducing agent and the specific mechanisms mediating the dose response. The hormetic dose response therefore represents a fundamental and broad strategy for regulatory maintenance and an adaptive resistance employed under stress-related conditions.

The significance of pre/post-conditioning is now widely recognized, with strong attempts being made to affect both clinical medicine and public health practices. Such activities involve both the chronic activation of conditioning mechanisms, as well as in attempts to regenerate/activate such processes which have been diminished by various co-morbidities (e.g. diabetes, atherosclerosis) and/or aging.

Of broad interest is the role of hormesis in natural selection/evolution. While hormesis/adaptive mechanisms are essential for survival, it is also evident that gradual diminution of such hormetic mechanisms across multiple systems will essentially lead to maladaptive responses and death. Hormesis is therefore essential for life and its erosion with aging along with its concomitant co-morbidities is a key factor affecting lifespan.

Biological systems typically display a limited plasticity that is described by the quantitative features of the hormetic dose response (Calabrese 2013a; Calabrese and Mattson 2011). There are therefore clear bounds within which adaptation and enhanced biological performance occur. Hormesis represents a gyroscopic-like function, providing a molecular/physiological navigation system, keeping the system on track (i.e., within the bounds of plasticity) and exhibiting moderate flexibility. While this plasticity conferring dose response process mediates optimal responsiveness, it also limits the extent to which biological performance can be enhanced. This highly selected and conserved plasticity limit places a significant biological constraint on what can be achieved via pharmacological intervention. It also places significant challenges when assessing performance-based drug efficacy within heterogeneous study subjects.

From a scientific perspective the modest amplitude of the low dose/concentration response set within a background of normal variability and within an historical framework in which high dose experimentation was widespread has been a significant factor obscuring the recognition of the hormetic-biphasic dose response as a central biological principle. This recognition was further blunted by the longstanding rivalry and conflicts between homeopathy and

Table 1 Hormesis characteristics

Hormetic dose responses are employed as a general biological regulatory strategy
Hormetic dose responses activate, strengthen and mediate a large number of biological processes, enhancing adaptability to endogenous and exogenous stressors
Hormetic/biphasic dose responses regulate and constrain the allocation of biological resources leading to optimal uses of limited cellular resources
Biological plasticity may be described by the quantitative features of the hormetic dose response
The quantitative features of the hormetic dose response are highly conserved, with similar strategies observed ranging from micro-organisms to humans
Hormetic dose responses act at multiple levels of biological organization, thereby synchronizing and integrating activities within the same quantitative scale
Hormetic dose responses are central components of normal development, growth, maintenance, repair and aging activities
Hormetic dose responses can also be part of disease processes as seen in adaptations of many tumor cells
Hormetic dose response is a fundamental biological adaptive process reflecting a cellular/metabolic gyroscopic-like function that provides the limits of plasticity with a flexible but limited dose response pattern. This biphasic dose response pattern is independent of species, and individual, regardless of developmental stage and gender, endpoint measured, mechanism and the inherent potency of the inducing agents. Evidence suggests that some hormetic pathways may become compromised in the elderly

traditional medicine which contributed in a significant way to the marginalizing of the hormetic dose response. These converging factors prevented an objective and substantial evaluation of the hormetic dose response throughout most of the twentieth century and also lead to an acceptance of alternative dose response models without proper validation. Thus, it is only within the past several decades in which the hormetic dose response has begun to be prospectively evaluated within a very broad biological and biomedical context, using rigorous study designs, and mechanistic evaluation.

Despite these exciting and notable advances, the concept of hormesis is still not widely known or ostensibly influential at the level of drug development, therapeutic application and within governmental regulatory programs. While the impact of hormesis in these respective domains seems negligible, this is actually not the case. For example, in the cases of anxiolytic (Calabrese 2008b), anti-seizure (Calabrese 2008c) and memory drugs (Calabrese 2008d), all essentially show an hormetic dose response in their preclinical testing. That is, these dose responses are hormetic. In practice, the optimal hormetic dose is selected for human trials. Most human trials, therefore, are based on the hormetic dose response without pharmaceutical companies nor federal regulatory agencies using the term or perhaps even being aware of the significance of this dose–response concept. This is also the case for the many applications of the pre- and post-conditioning concept to clinical medicine and public health. Thus, major segments of the biomedical and public health communities use the hormesis concept and derive their findings from it without perhaps knowing or fully appreciating it. There is evidence that such understandings and perceptions are changing.

The field of biogerontology is perhaps the one with the most extensive and broadest acculturation of the topic of hormesis. Such concept acceptance and integration can be traced to the influence of Professor Edward Masoro's (University of Texas at San Antonio) work on caloric restriction and his linking it to hormesis. While Masoro's first such paper was published in 1998, he cited several publications in the proceedings of the first hormesis conference about a decade earlier (Calabrese et al. 1987; Congdon 1987; Furst 1987). The 1998 paper of Masoro (1998) would be followed by several others by him of considerable influence, in 2000 (cited more than 400 times by mid-2015) (Masoro 2000) and in 2005 (cited more than 500 times by mid-2015) (Masoro 2005), with these papers being currently the fifth and second most cited papers in the Web of Science database on hormesis. The field has been also significantly affected by the research, publications and strong leadership of Suresh Rattan/Eric LeBourg in Europe, and Tom Johnson and Mark Mattson in the U.S., starting in the late 1990s as well.

Of note was the extension of the hormesis concept into the field of aging and neurodegenerative disease and neuroprotection as led by Mattson.

The leadership of the biogerontology field in the acceptance and extension of hormesis has been both by the use of the term and the extension of the concept. These two decades of leadership by aging-related research has made significant inroads for the concept of hormesis into many related biological and biomedical areas, although there is still limited knowledge, understanding and use of the term in many biomedical domains. In fact, there is still widespread use of alternative terms for what amounts to the same concept (e.g. biphasic, U-shaped, Hueppe's Law, Arndt-Schulz Law). For example, the term Arndt-Schulz Law remains widely used for application of laser induced biological effects such as wound healing acceleration principally because the initial significant scientific discoveries in this area were made in East Germany during the Cold War and Schulz worked at the University of Greifswald in East Germany. In fact, since language is important, a proposal to use a common similar terminology for similar biological stresses within a hormesis context was proposed in 2007 by nearly 60 researchers (Calabrese et al. 2007).

Final perspectives

In summary, the biological and biomedical sciences are in the midst of a dose response revolution in which the biphasic dose response which was rejected and marginalized by these fields nearly a century ago, has been found to occur often, reproducibly, with generality, and to have important applications especially in the area of therapeutics. It is also expected that the concept of hormesis will play a significant role in the public health domain as a component of lifespan enhancement practices increasing adaptive capacities that resist on the onset of acute and chronic diseases, including diabetes, cardiovascular diseases, neurodegenerative diseases and numerous others. Hormesis will be an important feature in all areas in which there is a need to improve biological performance such as in learning, athletics, sexual behavior, as well as areas such in the growing of hair and in the strengthening of bone. Hormesis should also have an important role in the area of environmental and occupational risk assessment of potentially harmful agents including carcinogens, reproductive toxins and the broad spectrum of regulated toxic substances. Substantial scientific literature already exists that documents each of these areas of hormesis significance. Since enhancing public health, biological performance and therapeutic efficacy are high priorities within society it is expected that the importance of the hormesis concept will continue to rapidly grow as well as its applications.

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Compliance with ethical standards

Conflict of Interest The authors declare no conflicts of interest.

Human and animal rights This research does not involve human or animal participants.

References

Abete P, Ferrara N, Cioppa A, Ferrara P, Bianco S, Calabrese C, Cacciatore F, Longobardi G, Rengo F (1996) Preconditioning does not prevent post-ischemic dysfunction in aging heart. J Am Coll Cardiol 27:1777–1786

Abete P, Ferrara N, Cacciatore F, Madrid A, Bianco S, Calabrese C, Napoli C, Scognamiglio P, Bollella O, Cioppa A, Longobardi G, Rengo F (1997) Angina-induced protection against myocardial infarction in adult and senescent patients. A loss of preconditioning mechanism in aging heart? J Am Coll Cardiol 30:947–954

Abete P, Calabrese C, Ferrara N, Cioppa A, Pisanelli P, Cacciatore F, Longobardi G, Napoli C, Rengo F (2000) Exercise training restores IP in the aging heart. J Am Coll Cardiol 36:643–650

Abete P, de Santis D, Condorelli M, Napoli C, Rengo F (2002a) A four-year-old rabbit cannot be considered the right model for investigating cardiac senescence. J Am Coll Cardiol 39:1701

Abete P, Testa G, Ferrara N, de Santis D, Capaccio P, Viati L, Calabrese C, Cacciatore F, Longobardi G, Condorelli M, Napoli C, Rengo F (2002b) Cardioprotec tive effect of IP is preserved in food-restricted senescent rats. Am J Physiol 282:H1978–H1987

Abete P, Cacciatore F, Testa G, Della-Morte D, Galizia G, de Santis D, Calabrese C, Cioppa A, Fewrrara N, Rengo F

(2010) Ischemic preconditioning in the aging heart: from bench to bedside. Age Res Rev 9:153–162
Ahuja A. (2003) Science: Some toxins may be good for us. London Times Online, 30
Ames BN (1987) 6 Common errors relating to environmental pollution. Regul Toxicol Pharmacol 7(4):379–383
Ames BN, Gold LS (1990) Chemical carcinogenesis—too many rodent carcinogens. Proc Natl Acad Sci USA 87(19): 772–776
Ames BN, Magaw R, Gold LS (1987) Ranking possible carcinogenic hazards. Science 236(4799):271–280
Bailey R. (2003) The dose makes the cure. Reason Online, March 12
Barrientos RM, Frank MG, Crysdale NY, Chapman TR, Ahrendsen JT, Day HEW, Campeau S, Watkins LR, Patterson SL, Maier SF (2011) Little exercise, big effects: reversing aging and infection-induced memory deficits, and underlying processes. J Neurosci 31(32):11578–11586
Bartling B, Friedrich I, Silber RE, Simm A (2003) IP is not cardioprotective in senescent human myocardium. Ann Thorac Surg 76:105–111
Begley S. (2003) Scientists revisit idea that a little poison could be beneficial. Wall Str J, Vol CCXLII (121)
Bell J. (2004) Can a low dose of poison be a good thing? Baltimore Sun, March 15
Bernstein RM (2010) The big and small of it: how body size evolves. Yearbook Phys Anthrpol 53:46–62
Bloedau CV (1884) General medical Central 93:1362
Boengler K, Konietzka I, Buechert A, Heinen Y, Garcia-Dorado D, Heusch G, Schulz R (2007) Loss of IP's cardioprotection in aged mouse hearts is associated with reduced gap junctional and mitochondrial levels of connexin 43. Am J Physiol Heart Circ Physiol 292:H1764–H1769
Bohme H. (1986) Hugo Schulz (8/6/1853-7/13/1932). His life and work, Ph.D. thesis, Freien University of Berlin. Berlin, Germany
Boyce N. (2004) Is there a tonic in the toxin? U.S. News and World Report, October 18
Burns PG, Krukenkamp IB, Caldarone CA, Kirvaitis RJ, Gaudette GR, Levitsky S (1996) Is the preconditioning response conserved in senescent myocardium? Ann Thorac Surg 61(3):925–929
Calabrese EJ (1999) Evidence that hormesis represents an "overcompensation" response to a disruption in homeostasis. Ecotoxicol Environ Saf 42:135–137
Calabrese EJ (2001a) Overcompensation stimulation: a mechanism for hormetic effects. Crit Rev Toxicol 31:425–470
Calabrese EJ (2001b) Prostaglandins: biphasic dose responses. Crit Rev Toxicol 31:475–487
Calabrese EJ (2001c) Estrogen and related compounds: biphasic dose responses. Crit Rev Toxicol 31:503–515
Calabrese EJ (2001d) Androgens: biphasic dose responses. Crit Rev Toxicol 31:517–522
Calabrese EJ (2001e) Adrenergic receptors: biphasic dose responses. Crit Rev Toxicol 31:523–538
Calabrese EJ (2001f) Adenosine: biphasic dose responses. Crit Rev Toxicol 31:539–551
Calabrese EJ (2001g) 5-hydroxytryptamine (serotonin): biphasic dose responses. Crit Rev Toxicol 31:553–561
Calabrese EJ (2001h) Dopamine: biphasic dose responses. Crit Rev Toxicol 31:563–583
Calabrese EJ (2001i) Opiates: biphasic dose responses. Crit Rev Toxicol 31:585–604
Calabrese EJ (2004) Hormesis: from marginalization to mainstream. A case for hormesis as the default dose-response model in risk assessment. Toxicol Appl Pharmacol 197: 125–136
Calabrese EJ (2005a) Historical blunders: how toxicology got the dose-response relationship half right. Cell Mol Biol 51:643–654
Calabrese EJ (2005b) Toxicological awakenings: the rebirth of hormesis as a central pillar of toxicology. Toxicol Appl Pharmacol 204:1–8
Calabrese EJ (2007) Converging concepts: adaptive response, preconditioning, and the Yerkes-Dodson law are manifestations of hormesis. Aging Res Rev 7:8–20
Calabrese EJ (2008a) Hormesis and medicine. Br J Clin Pharmacol 66:594–617
Calabrese EJ (2008b) An assessment of anxiolytic drug screening tests: hormetic dose responses predominate. Crit Rev Toxicol 38(6):489–542
Calabrese EJ (2008c) Modulation of the epileptic seizure threshold: implications of biphasic dose responses. Crit Rev Toxicol 38(6):543–556
Calabrese EJ (2008d) Alzheimer's disease drugs: an application of the hormetic dose-response model. Crit Rev Toxicol 38(5):419–451
Calabrese EJ (2008e) Dose-response features of neuroprotective agents: an integrative summary. Crit Rev Toxicol 38(4):249–252
Calabrese EJ (2008f) Hormesis: why it is important to toxicology and toxicologists. Environ Toxicol Chem 27(7):1451–1474
Calabrese EJ (2009a) The road to linearity: why linearity at low doses became the basis for carcinogen risk assessment. Arch Toxicol 83(3):203–225
Calabrese EJ (2009b) Getting the dose-response wrong: why hormesis became marginalized and the threshold model accepted. Arch Toxicol 83(3):227–247
Calabrese EJ (2010) Hormesis is central to toxicology, pharmacology and risk assessment. Hum Exper Toxicol 29:249–261
Calabrese EJ (2011) Toxicology rewrites its history and rethinks its future: giving equal focus to both harmful and beneficial effects. Environ Toxicol Chem 30(12):2658–2673
Calabrese EJ (2012) Hormesis: why it is important to biogerontologists. Biogerontology 13:215–235
Calabrese EJ (2013a) Biphasic dose response in biology, toxicology and medicine: accounting for their generalizability and quantitative features. Environ Poll 182:452–460
Calabrese EJ (2013b) Hormetic mechanisms. Crit Rev Toxicol 43(7):580–606
Calabrese EJ (2013c) Low doses of radiation can enhance insect lifespans. Biogerontology 14(4):365–381
Calabrese EJ, Baldwin LA (2000a) Chemical hormesis: its historical foundations as a biological hypothesis. Hum Exper Toxicol 19(1):2–31
Calabrese EJ, Baldwin LA (2000b) The marginalization of hormesis. Hum Exper Toxicol 19(1):32–40
Calabrese EJ, Baldwin LA (2000c) Radiation hormesis: its historical foundations as a biological hypothesis. Hum Exper Toxicol 19(1):41–75

Calabrese EJ, Baldwin LA (2000d) Radiation hormesis: the demise of a legitimate hypothesis. Hum Exper Toxicol 19(1):76–84

Calabrese EJ, Baldwin LA (2000e) Tales of two similar hypotheses: the rise and fall of chemical and radiation hormesis. Hum Exper Toxicol 19(1):85–97

Calabrese EJ, Baldwin LA (2000f) The effects of gamma rays on longevity. Biogerontology 1(4):309–319

Calabrese EJ, Baldwin LA (2001a) Scientific foundations of hormesis. Crit Rev Toxicol 31:349–695

Calabrese EJ, Baldwin LA (2001b) Agonist concentration gradients as a generalizable regulatory implementation strategy. Crit Rev Toxicol 31(4–5):471–473

Calabrese EJ, Baldwin LA (2002) Defining hormesis. Hum Exp Toxicol 21:91–97

Calabrese EJ, Baldwin LA (2003a) Toxicology rethinks its central belief: hormesis demands a reappraisal of the way risks are assessed. Nature 42:691–692

Calabrese EJ, Baldwin LA (2003b) The hormetic dose-response model is more common than the threshold model in toxicology. Toxicol Sci 71:246–250

Calabrese EJ, Blain R (2005) The occurrence of hormetic dose responses in the toxicological literature, the hormesis database: an overview. Toxicol Appl Pharmacol 202:289–301

Calabrese EJ, Blain RB (2009) Hormesis and plant biology. Environ Poll 157(1):42–48

Calabrese EJ, Blain RB (2011) The hormesis database: the occurrence of hormetic dose response in the toxicological literature. Regul Toxicol Pharmacol 61(1):73–81

Calabrese EJ, Mattson MP (2011) Hormesis provides a generalized quantitative estimate of biological plasticity. J Cell Comm Signal 5(1):25–38

Calabrese EJ, McCarthy ME, Kenyon E (1987) The occurrence of chemically-induced hormesis. Health Phys 52(5):531–541

Calabrese EJ, Staudenmayer JW, Stanek EJ III, Hoffmann GR (2006) Hormesis outperforms threshold model in National Cancer Institute antitumor drug screening database. Toxicol Sci 94(2):368–378

Calabrese EJ, Bachmann KA, Bailer AJ, Bolger PM, Borak J, Cai L, Cedergreen N, Cherian MG, Chiueh CC, Clarkson TW, Cook RR, Diamond DM, Doolittle DJ, Dorato MA, Duke SO, Feinendegen L, Gardner DE, Hart RW, Hastings KL, Hayes AW, Hoffmann GR, Ives JA, Jaworowski Z, Johnson TE, Jonas WB, Kaminski NE, Keller JG, Klaunig JE, Knudsen TB, Kozumbo WJ, Lettieri T, Liu S-Z, Maisseu A, Maynard KI, Masoro EJ, McClellan RO, Mehendale HM, Mothersill C, Newlin DB, Nigg HN, Oehme FW, Phalen RF, Philbert MA, Rattan SIS, Riviere JE, Rodricks J, Sapolsky RM, Scott BR, Seymour C, Sinclair DA, Smith-Sonneborn J, Snow ET, Spear L, Stevenson DE, Thomas Y, Tubiana M, Gem Williams, Mattson MP (2007) Biological stress response terminology: integrating the concepts of adaptive response and preconditioning stress within a hormetic dose–response framework. Toxicol Appl Pharmacol 222:122–128

Calabrese EJ, Stanek EJ III, Nascarella MA, Hoffmann GR (2008) Hormesis predicts low dose-responses better than threshold models. Intl J Toxicol 27:369–378

Calabrese EJ, Hoffmann GR, Stanek EJ III, Nascarella MA (2010) Hormesis in high-throughput screening of antibacterial compounds in *E. coli*. Hum Exp Toxicol 29:667–677

Chrysostomou V, Kezic JM, Trounce IA, Crowston JG (2014) Forced exercise protects the aged optic nerve against intraocular pressure injury. Neurobiol Aging 35:1722–1725

Clark AJ (1933) Mode of action of drugs on cells. Arnold, London

Clark AJ (1937) General pharmacology. In: Hefftner AJ (ed) Handbuch der Experimentellen Pharmakologie (Handbook of Experimental Pharmacology). Verlig Von Julius Springer, Berlin

Congdon CC (1987) A review of certain low-level ionizing radiation studies in mice and guinea pig. Health Phys 52:593–597

Cook G (2003) A scientist finds benefit in small doses of toxins. Boston Globe 12:A16–A18

Cork JM (1957) Gamma-radiation and longevity of the flour beetle. Radiat Res 7:551–557

Costantini D (2014) Oxidative stress and hormesis in evolutionary ecology and physiology. A marriage between mechanistic and evolutionary approaches. Springer, Berlin

Coulter HL (1972) Homoeopathic medicine. Formur, St. Louis

Coulter HL (1982) Divided legacy: the conflict between homoeopathy and the American Medical Association. North Atlantic Books, Berkeley

Crump T (2003) Contemporary medicine as presented by its practitioners themselves. Leipzig, 1923:217-250, Hugo Schulz, NIH Library Translation (NIH-98-134). Nonlinear Biol Toxicol Med 1:295–318

Cypser JR, Johnson TE (2002) Multiple stressors in *Caenorhabditis elegans* induce stress hormesis and extended longevity. J Gerontol Ser A 57(3):B109–B114

Davey WP (1917) The effect of X-rays on the length of life of *Tribolium confusum*. J Exp Zool 22(3):573–592

Davey WP (1919) Prolongation of life of *Tribolium confusum* apparently due to small doses of X-rays. J Exp Zool 28(3):447–458

Demirovic D, Rattan SIS (2011) Curcumin induces stress response and hermetically modulates wound healing ability of human skin fibroblasts undergoing ageing in vitro. Biogerontology 12:437–444

Ebrahim Z, Yellon DM, Baxter GF (2007) IP is lost in aging hypertensive rat heart: independent effects of aging and longstanding hypertension. Exp Gerontol 42:807–814

Elliott KC (2011) Is a little pollution good for you? Incorporating societal values into environmental research. Oxford University Press, London

Fenton RA, Dickson EW, Meyer TE, Dobson JG Jr (2000) Aging reduces the cardioprotective effect of IP in the rat heart. J Mol Cell Cardiol 32:1371–1375

Fosslien E (2002) Establishment, maintenance, and remodeling of curvature in biology. Med Hypotheses 59(3):233–238

Fosslien E (2009) The hormetic morphogen theory of curvature and the morphogenesis and pathology of tubular and other curved structures. Dose Response 7(4):307–331

Furst A (1987) Hormetic effects in pharmacology—pharmacological inversions as prototypes for hormesis. Health Phys 52(5):527–530

Gadhia PK (1998) Possible age-dependent adaptive response to a low dose of X-rays in human lymphocytes. Mutagenesis 13(2):151–152

Garcia-Mesa Y, Pareja-Galeano H, Bonet-Costa V, Revilla S, Gomez-Cabrera MC, Gambini J, Gimenez-Llort L, Cristofol R, Vina J, Sanfeliu C (2014) Physical exercise neuroprotects ovariectomized 3xTg-AD mice through BDNF mechanisms. Psychoneuroendocrinology 45:154–166

He Z, Meschia JF, Brott TG, Dickson DW, McKinney M (2006) Aging is neuroprotective during global ischemia but leads to increased caspase-3 and apoptotic activity in hippocampal neurons. Curr Neurovasc Res 3(3):181–186

He Z, Crook JE, Meschia JF, Brott TG, Dickson DW, McKinney M (2015) Aging blunts ischemic-preconditioning-induced neuroprotection following transient global ischemia in rats. Curr Neurovasc Res 2(5):365–374

Heusch G, Botker HE, Przyklenk K, Redington A, Yellon D (2015) Remote ischemic conditioning. J Am Coll Cardiol 65(2):177–195

Hively W. (2003) Is radiation good for you? Discover, 74–80

Hunt PR, Son TG, Wilson MA, Yu Q-S, Wood WH, Zhang Y, Becker KG, Greig NH, Mattson MP, Camandola S, Wolkow CA (2011) Extension of lifespan in *C. elegans* by naphthoquinones that act through stress hormesis mechanisms. PLoS One 6(7):e21922

Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Nishioka K, Kouno Y, Umemura T, Nakamura S, Sato H (2001) Diabetes mellitus prevents ischemic preconditioning in patients with a first acute anterior wall myocardial infarction. J Am Coll Cardiol 38:1007–1011

Jahangir A, Sagar S, Terzic A (2007) Aging and cardioprotection. J Appl Physiol 103:2120–2128

Kahn A, Olsen A (2010) Stress to the rescue: is hormesis a 'cure' for aging? Dose Response 8(1):48–52

Kaiser J (2003) Sipping from a poisoned chalice. Science 302:276–279

Kitani K, Minami C, Isobe K-I, Maehara K, Kanai S, Ivy GO, Carrillo M-C (2002) Why (-)deprenyl prolongs survivals of experimental animals: increase of antioxidant enzymes in brain and other body tissues as well as mobilization of various humoral factors may lead to systemic anti-aging effects. Mech Ageing Dev 123:1087–1100

Kitani K, Kanai S, Miyasaka K, Carrillo M-C, Ivy GO (2005) Dose-dependency of life span prolongation of F344/DuCrj rats injected with (-)deprenyl. Biogenerontol 6:297–302

Krenz M, Baines C, Kalogeris T, Korthuis RJ. (2013) Cell survival programs and ischemia/reperfusion. Hormesis, preconditioning, and cardioprotection. In: Granger DN & Granger J (ed) Colloquium series on integrated systems physiology: from molecule to function to disease, Lecture #44, Digital Library. Morgan & Claypool Life Sciences

Kubo M, Li T-S, Kurazumi H, Takemoto Y, Ohshima M, Murata T, Katsura S, Morikage N, Furutani A, Hamano K (2012) Hypoxic preconditioning enhances angiogenic potential of bone marrow cells with aging-related functional impairment. Circ J 76:986–994

Kwak HB, Song W, Lawler JM (2006) Exercise training attenuates age-induced elevation in Bax/Bcl-2 ratio, apoptosis, and remodeling in the rat heart. FASEB J 20:791–793

Lambert E (2003) A pinch of poison. Forbes Life Online 22:236–237

Le Bourg E (2011) Using *Drosophila melanogaster* to study the positive effects of mild stress on aging. Exp Gerontol 46:345–348

Le Bourg E, Rattan S (2009) Mild stress in healthy aging: applying hormesis in aging research and interventions. Springer, New York

Lee TM, Su SF, Chou TF, Lee YT, Tsai CH (2002) Loss of preconditioning by attenuated activation of myocardial ATP-sensitive potassium channels in elderly patients undergoing coronary angioplasty. Circulation 105:334–340

Lehman AJ, Fitzhugh OG (1953) 100-fold margin of safety. Assoc Food Drug Off Quart Bull 17(2):33–35

Long P, Nguyen Q, Thurow C, Broderick TL (2002) Caloric restriction restores the cardioprotective effect of preconditioning in the rat heart. Mech Ageing Dev 123:1411–1443

Longobardi G, Abete P, Ferrara N, Papa A, Rosiello R, Furgi G, Calabrese C, Cacciatore F, Rengo F (2000) "Warm-up" phenomenon in adult and elderly patients with coronary artery disease: further evidence of the loss of "IP" in the aging heart. J Gerontol A 55:M124–M129

Loubani M, Ghosh S, Galinanes M (2003) The aging human myocardium: tolerance to ischemia and responsiveness to ischemic preconditioning. J Thorac Cardiovasc Surg 126(1):143–147

Lu R, Hu CP, Deng HW, Li YJ (2001) Calcitonin gene-related peptide-mediated IP in the rat heart: influence of age. Regul Pept 99:183–189

Luckey TD (1980) Hormesis with ionizing radiation. CRC, Boca Raton

Luckey TD (1991) Radiation hormesis. CRC, Boca Raton

Luckey TD, Venugopal V, Hutcheson D (1975) Heavy metal toxicity, safety and hormology. Academic Press, New York

Marques FZ, Markus MA, Morris BJ (2010) Hormesis as a pro-health aging intervention in human beings? Dose Response 8(1):28–33

Masoro EJ (1998) Hormesis and the antiaging action of dietary restriction. Exp Gerontol 33(1–2):61–66

Masoro EJ (2000) Caloric restriction and aging: an update. Exp Gerontol 35(3):299–305

Masoro EJ (2005) Overview of caloric restriction and ageing. Mech Ageing Dev 126(9):913–922

Mattson M, Calabrese EJ (2010) Hormesis: a revolution in biology, toxicology and medicine. Springer, New York

McCully JD, Uematsu M, Parker RA, Levitsky S (1998) Adenosine-enhanced IP provides enhanced cardioprotection in the aged heart. Ann Thorac Surg 66:2037–2043

Meng R, Ding Y, Asmaro K, Brogan D, Meng L, Sui M, Shi J, Duan Y, Sun Z, Yu Y, Jia J, Ji X (2015) Ischemic conditioning is safe and effective for octo- and nonagenarians in stroke prevention and treatment. Neurotherapeutics 12:667–677

Miura Y (2004) Oxidative stress, radiation-adaptive responses, and aging. J Radiat Res 45:357–372

Miura Y, Endo T (2010) Survival responses to oxidative stress and aging. Geriatr Gerontol Int 10(Suppl 1):S1–S9

Miura Y, Abe K, Urano S, Furuse T, Noda Y, Tatsumi K, Suzuki S (2002) Adaptive response and the influence of ageing: effects of low-dose irradiation on cell growth of cultured glial cells. Int J Radiat Biol 78(10):913–921

Murry CE, Jennings RB, Reimer KA (1986) Preconditioning with ischemia—a delay of lethal cell injury in ischemic myocardium. Circulation 74:1124–1136

Napoli C, Liguori A, Cacciatore F, Rengo F, Ambrosio G, Abete P (1999) Warm-up phenomenon detected by electrocardiographic ambulatory monitoring in adult and older patients. J Am Geriatr Soc 47:1114–1117

Newton IG, Forbes ME, Linville MC, Pang H, Tucker EW, Riddle DR, Brunso-Bechtold JK (2008) Effects of aging and caloric restriction on dentate gyrus synapses and glutamate receptor subunits. Neurobiol Aging 29:1308–1318

O'Brien JD, Howlett SE (2008) Simulated ischemia-induced preconditioning of isolated ventricular myocytes from young adult and aged Fischer-344 rat hearts. Am J Physiol Heart Circ Physiol 295:H768–H777

Olsen A, Vantipalli MC, Lithgow GJ (2006) Lifespan extension of *Caenorhabditis elegans* following repeated mild hormetic heat treatments. Biogerontology 7(4):221–230

Pardon MC (2010) Hormesis is applicable as a pro-health aging intervention in mammals and human beings. Dose Response 8(1):22–27

Park S (2010) Effect of preconditioning regular exercise on ischemic stroke in aged brain. J Exerc Nutr Biochem 14(1):39–43

Pepe S (2001) Dysfunctional IP mechanisms in aging. Cardiovasc Res 49:11–14

Pike J. (2004) Can toxins lead to healthier lives? Insight Magazine, 6

Powers SK, Quindry J, Hamilton K (2004) Aging, exercise, and cardioprotection. Ann NY Acad Sci 019:42–470

Raloff J (2007) Counterintuitive toxicity. Science News Online 171:40

Rattan SIS (2012) Rationale and methods of discovering hormetins as drugs for healthy ageing. Expert Opin Drug Discov 7(5):439–448

Rattan SIS, Le Bourg E (2014) Hormesis in health and disease. CRC Press, Boca Raton

Renner R (2003) Hormesis: Nietzsche's toxicology. Sci Am. 289:28–30

Ristow M, Schmeisser S (2011) Extending life span by increasing oxidative stress. Free Radic Biol Med 51(2): 327–336

Roberge M-C, Messier C, Staines WA, Plamondon H (2008) Food restriction induces long-lasting recovery of spatial memory deficits following global ischemia in delayed matching and non-matching-to-sample radial arm maze tasks. Neuroscience 156:11–29

Roberts R. (2003) Here's to your health. St. Louis Post Dispatch, January 9

Rohrbach S, Aslam M, Niemann B, Schulz R (2014) Impact of caloric restriction on myocardial ischaemia/reperfusion injury and new therapeutic options to mimic its effects. Brit J Pharmacol 171:2964–2992

Sagan LA (1989) On radiation, paradigms, and hormesis. Science 245(4918):574–621

Salminen A, Kaarniranta K (2010) ER stress and hormetic regulation of the aging process. Ageing Res Rev 9(3): 211–217

Sarup P, Loeschcke V (2011) Life extension and the position of the hormetic zone depends on sex and genetic background in *Drosophila melanogaster*. Biogerontology 12:109–117

Saunders C (2010) Radiation hormesis and the linear no-threshold assumption. Springer, New York

Schulman D, Latchman DS, Yellon DM (2001) Effect of aging on the ability of preconditioning to protect rat hearts from ischemia-reperfusion injury. Am J Physiol 28:H1630–H1636

Schulz H (1887) Zur Lehre von der Arzneiwirkung. Virchows Arch Pathol Anat Physiol Klin Med 108:423–445

Schulz H (1888) Uber Hefegifte. Pflugers Archiv—fur die gesamte Physiologie des Menschen und der Tiere 42:517–541

Shackell LF (1923) Studies in protoplasm poisoning I. Phenols. J Gen Physiol 5:783–805

Shackell LF (1925) The relation of dosage to effect II. J Pharmacol Exp Ther 15:275–288

Shackell LF, Williamson W, Deitchmann MM, Katzman GM, Dleinman BS. (1924/1925) The relation of dosage to effect. J Pharmacol Exp Ther 23–24:53–56

Southam CM, Erhlich J (1943) Effects of extracts of western red-cedar heartwood on certain wood-decaying fungi in culture. Phytophathology 33:517–524

Stebbing ARD (1976) Effects of low metal levels on a clonal hydroid. J Marine Biol Assoc UK 56(4):977–994

Stebbing ARD (1982) Hormesis—the stimulation of growth by low-levels of inhibitors. Sci Total Environ 22(3):213–234

Stebbing ARD (1987) Growth hormesis—a by-product of control. Health Phys 52:543–547

Stebbing ARD (1998) A theory for growth hormesis. Mutat Res 403:249–258

Stebbing A (2011) A cybernetic view of biological growth: the Maia hypothesis. Cambridge Publishers, London

Stipp D (2003) A little poison can be good for you. Fortune 147:54–55

Szabadi E (1977) A model of two functionally antagonistic receptor populations activated by the same agonist. J Theor Biol 69:101–112

Tani M, Suganuma Y, Hasegawa H, Shinmura K, Hayashi Y, Guo X, Nakamura Y (1997) Changes in ischemic tolerance and effects of IP in middle-aged rat hearts. Circulation 95:2559–2566

Tesic V, Perovic M, Lazic D, Kojic S, Smiljanic K, Ruzdijic S, Rakic L, Kanazir S (2015) Long-term intermittent feeding restores impaired GR signaling in the hippocampus of aged rat. J Ster Biochem Mol Biol 49:43–52

Vasconcelos AR, Kinoshita PF, Yshii LM, Orellana AMM, Bohmer AE, de Sa Lima L, Alves R, Andreotti DZ, Marcourakis T, Scavone C, Kawamoto EM (2015) Effects of intermittent fasting on age-related changes on Na, K-ATPase activity and oxidative status induced by lipopolysaccharide in rat hippocampus. Neurobiol Aging 36:1914–1923

Wels P (1933) The life time work of Hugo Schulz. Naunyn-Schmiedebergs Arch Pharmakol 170:744–757

Wolff S (1989) Are radiation-induced effects hormetic. Science 245(4918):575–621

Yin Z, Gao H, Wang H, Li L, Di C, Luan R, Tao L (2009) Ischaemic post-conditioning protects both adult and aged Sprague-Dawley rat heart from ischaemia-reperfusion injury through the phosphatidylinositol 3-kinase-Akt and glycogen synthase kinase-3β pathways. Clin Exp Pharmacol Physiol 36:756–763