

Getting the dose–response wrong: why hormesis became marginalized and the threshold model accepted

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Abstract The dose–response relationship is central to the biological and biomedical sciences. During the early decades of the twentieth century consensus emerged that the most fundamental dose–response relationship was the threshold model, upon which scientific, health and medical research/clinical practices have been based. This paper documents that the scientific community made a fundamental error on the nature of the dose response in accepting the threshold model and in rejecting the hormetic-biphasic model, principally due to conflicts with homeopathy. Not only does this paper detail the underlying factors leading to this dose response decision, but it reveals that the scientific community never validated the threshold model throughout the twentieth century. Recent findings indicate that the threshold model poorly predicts responses in the low dose zone whereas its dose response “rival”, the hormesis model, has performed very well. This analysis challenges a key foundation upon which biological, biomedical and clinical science rest.

Keywords Hormesis · Hormetic · Threshold · Biphasic · U-shaped · J-shaped

Introduction

This paper deals with how key leaders of the biomedical sciences made a profound error on a fundamental scientific concept, that is, the nature of the dose response, a central

pillar of pharmacology, toxicology and clinical medicine. In the 1930s the scientific community consolidated its conceptual understanding of the nature of the dose response, building its scientific programs around the threshold dose response model, a model that would come to guide how biological models are selected, studies are designed, data are statistically analyzed and modeled, how safe and effective doses of drugs are determined, how environmental, occupational and consumer exposure standards are derived and how risks and benefits are assessed. In short, getting the dose response model correct is a basic necessity for society.

It is the contention of this paper that the scientific community made a critical mistake on the adoption of the threshold model, a mistake that was used as an ill advised tool of modern “traditional medicine” to help defeat a former powerful financial opponent, the medical practice of homeopathy. To make a bad situation worse, intellectual leaders of the “traditional medicine” movement, that is, leading pharmacologists and toxicologists of the 1930s and for the rest of the twentieth century, for that matter, never attempted to validate the capacity of their model, (i.e., society’s model), to make accurate predictions where it really counts, in the low dose zone where people live. When the threshold dose response model was finally tested for its capacity to make accurate predictions in the low dose zone, it miserably failed (Calabrese and Baldwin 2003; Calabrese and Baldwin 2001; Calabrese et al. 2006). In the ultimate of scientific ironies the model that leaders of pharmacology and toxicology rejected in the 1930s, that is, the hormetic dose response, performed extremely well in these low dose validation studies, leading one to fairly conclude that a fundamental and continuing mistake had been made on the selection of the dose response model that has been guiding innumerable public health and medical decisions for the last three

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quarters of a century. This article will address how this extraordinary error was made, missed and perpetuated.

Hormesis defined

Hormesis is a dose–response relationship characterized by a low dose stimulation and a high dose inhibition. The hormetic dose response has been typically represented in graphs as an inverted U- or J-shaped dose response, depending on the endpoint measured. For example, in the cases of growth, cell proliferation, memory and longevity, hormetic responses have typically been graphed as an inverted U-shaped dose response. In the case of endpoints such as disease incidence (e.g., tumor formation, cardiovascular disease, genotoxicity, birth defects), hormetic effects are typically graphed as a J-shaped dose response (Fig. 1). However, this broad range of inverted U- and J-shaped dose response relationships are all considered examples of hormesis.

Origin of the term hormesis

The term hormesis, meaning to excite in Greek, is now 65 years old, having been first reported in the peer-reviewed scientific literature in 1943 by Chester Southam and John Ehrlich, then researching the effects of extracts of the red cedar tree on the metabolism of a number of fungal strains in hopes of better understanding factors that affect fungal-induced wood rotting. Southam and Ehrlich would soon leave the field of forestry for the biomedical sciences where Ehrlich was to become a co-discoverer of antibiotic chloramphenicol (Ehrlich et al. 1948) and Southam would

come to direct notable research on immune recognition of tumor antigens (Southam 1967a, b).

Hugo Schulz and the hormesis concept

While credit for the name hormesis remains that of Southam and Ehrlich, the “concept” embodied in the term is much older. Credit for this concept is usually reserved for Hugo Schulz (1853–1932), a pharmacologist at the University of Greifswald, for research initially conducted on the effects of disinfectants on yeast metabolism in the mid 1880s (Schulz 1887, 1888) and for the creation of an integrated dose response concept that he co-developed with Rudolph Arndt, a psychiatrist at Greifswald. The extensive promotion of their dose response concept led to the Arndt-Schulz Law, the first of many terms to describe this dose response concept. Independently of Schulz and Arndt, the bacteriologist protégé of Robert Koch, Ferdendane Hueppe, also developed a similar dose response theory based on his own laboratory findings with bacteria, leading to the creation of another early term, Hueppe’s Rule, for the same concept (Hueppe 1896). Yet behind the thinking of both Schulz/Arndt and Hueppe were underlying physiological concepts (i.e. convulsion law) of Pfulger upon which their concepts were based (Bohme 1986).

Despite the search for whom credit should go for introducing the concept of biphasic dose responses to the biological and biomedical fields, it was the near 40 years of passionate professional commitment to this concept by Schulz, until his death in 1932, that provided both the support to develop this concept further and his inappropriate linkage of this concept to the field of homeopathy that undercut much of his professional achievements that supported the hormesis concept (Calabrese 2005). In fact, the linkage of this dose–response concept to homeopathy had a devastating impact not only on the concept of hormesis but surprisingly harmful effects on the biomedical sciences, including pharmacology and its clinical applications as these fields did what they could to deny hormesis, thereby losing benefits this concept would have contributed. Why did Schulz link his research findings that low doses of numerous disinfectants biphasically affected yeast metabolism to homeopathy? Why did he claim that these findings provided the explanatory principle upon which homeopathy was based?

In the early 1880s Schulz became aware of several published studies indicating that the homeopathic drug, veratrine (i.e., a mixture of alkaloids from the white hellebore), was successfully employed in the treatment of gastroenteritis (Schulz 1885). Since the bacteria causing this condition had been recently identified by Koch’s laboratory, Schulz assessed whether veratrine would be toxic to the bacteria

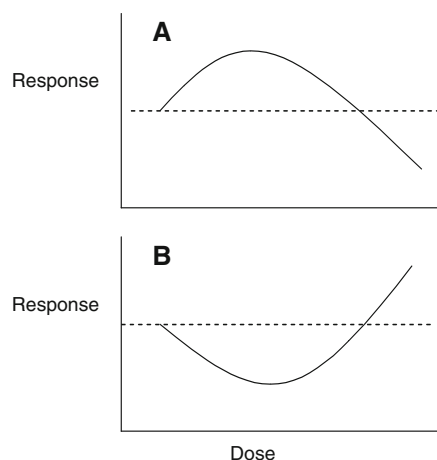


Fig. 1 A general representation of the hormetic dose–response. **a** The most common form of the hormetic dose–response curve depicting low-dose stimulatory and high-dose inhibitory responses, the β - or inverted U-shaped curve. **b** The hormetic dose–response curve depicting low-dose reduction and high-dose enhancement of adverse effects, the J- or U-shaped curve

when cultured. His testing revealed that the drug was unable to kill the harmful bacteria regardless of the dose used. Since he believed this drug was effective when clinically employed, he concluded that it must act via an alternative mechanism than directly killing the bacteria. His chance to provide that alternative explanation presented itself several years later when he observed that numerous chemical disinfectants were able to stimulate yeast metabolism at low concentrations while being inhibitory at higher doses (Schulz 1888). He used these specific observations to offer a generalized dose response theory that low doses of stressor agents induced adaptive responses, while at higher doses they may be harmful. He speculated that this must be how the veratrine successfully cured the affected patients and was how other homeopathic drugs may work.

As Schulz quickly became aligned with the medical practice of homeopathy he became the target of criticism of those associated with what is now called traditional medicine. As early as 1896, in his major text *Principles of Bacteriology*, Hueppe acknowledged the reproducibility of the dose response data of Schulz, indicating that this work should not be dismissed even though it had been used to support homeopathic interpretations. However, as history would show, others would not be so intellectually tolerant.

The demise of the hormesis concept

The conflict between homeopathy and traditional medicine was intense and prolonged. It was a conflict over principle, science, power and money. Since Schulz had taken sides he and his dose response theory became “fair-game” and the object of much criticism by the intellectual elite within the traditional medicine group, in fact, the forerunners of modern pharmacology and toxicology. As I have indicated previously (Calabrese 2005), the most effective, persistent, influential and respected critic was Alfred J. Clark, a leading UK pharmacologist with professorships at the University of London and finally at Edinburgh. Clark was recognized as a leader in the field of quantitative pharmacology, a co-founder of the British Society of Pharmacology, author of several extremely influential textbooks and one who certainly cast a broad and influential shadow across the field. The criticisms of Clark upon the work of Schulz were timed perfectly as far as traditional medicine was concerned. That is, it covered the time after Schulz had retired, was less able to defend his positions, and when Clark’s reputation was substantial. At the same time homeopathy had taken serious criticism in the US following the Flexner Report (Flexner 1910), with support for it in a marked downward spiral. The essence of Clark’s criticism was that the biphasic dose response of Schulz was often not reproducible and

whenever it was reproducible it was of trivial importance. He then linked Schulz with the high dilutionist-wing of the homeopathy movement, a linkage that is not supported in the literature (Calabrese 2005), in order to further marginalize the man and his ideas.

The criticisms of Clark (1927, 1933, 1937) struck at the same time that the dose response concept was being consolidated within the scientific community, governmental regulatory agencies, and in academic institutions. The strategy that unfolded was that an alternative dose–response model to Schulz’s biphasic dose response model needed to be codified and adopted that would guide study designs, safety evaluations and modern risk assessment. The choice was easy. It was the threshold dose response model, a model that had scientific support in literature (Shackell 1923, 1925, 1924/1925) and around which Clark’s books were framed. Even more ingenious was that the highly esteemed biostatistician Ronald Fisher merged the concept of the maximum likelihood estimate (see Bliss 1935c) to the recently created probit model of Clark’s colleagues Gaddum (1933) and Bliss (1935a, b, c) in the early to mid 1930s. This resulted in constraining the dose response curve to approach but to never go below the control value, thereby denying the possibility of Schulz’s biphasic dose response. So successful were these pharmacological/toxicological “chess moves” that they became the core of academic teaching, research and governmental risk assessment methods, even to the present. So eager were the opponents of Schulz’s biphasic dose response model to adopt an alternative model (i.e., the threshold model) that they never attempted to validate predictions of that model in the critical zone below the threshold, the zone where most people live, that is, exposed to low levels of chemical agents and environmental radiation. While it is difficult to believe that the principal model upon which most chemical safety decisions were based in all modern industrialized countries was never tested for validation, there is no evidence that it ever was. Some 70 years would pass until such validation studies were made (Calabrese and Baldwin 2001, 2003; Calabrese et al. 2006). The results were not very flattering to the threshold model as it strikingly and consistently failed to accurately predict responses below the pharmacologic and toxicologic thresholds. The failure of the threshold dose response model to be validated for its capacity to accurately predict low dose responses across biological models, endpoints and chemical classes now represents a serious issue for medicine, pharmacology, toxicology, risk assessment and society itself since this model has long served as the principal societal default model upon which many environmental standards, drug safety evaluations, medical treatments, and societal risk communication have been based.

The biphasic dose response model of Schulz therefore became marginalized from the centrality of scientific and

biomedical developments during the 1930s. Such marginalization has continued to impact biological/biomedical disciplines to the present. This is reflected in the long-term exclusion of the hormesis term from major textbooks, academic teaching, governmental research, funding, professional society meetings and governmental regulatory practices. This was quietly and brilliantly achieved with neither any commotion or scientific debate, and all within the openness of western countries. In effect, the hormesis concept was given a near scientific death sentence.

Despite this “near death sentence” manuscripts with examples of hormetic-like biphasic dose responses were continually published throughout the twentieth century under the guise of various terms, or without any acknowledgement by the authors. In fact, Calabrese and Baldwin (2000a, b, c, d, e) documented numerous publications supportive of the hormetic dose response concept from the late decades of the nineteenth century to mid 1940s when the dose response concept consolidation was becoming essentially complete. Thus, one must wonder how it was possible to profoundly marginalize a scientific concept that was widely reported in reputable journals and by some notable scientists. That is, even though “traditional medicine” employed many means to defeat homeopathy, including efforts to minimize Schulz and his dose response theory and sought to replace the biphasic dose response model that we now call hormesis with the threshold model, there were other contributory factors that facilitated this toxicological dose–response intellectual and functional coup. They include: (1) a failure of scientific leaders to challenge the dominance of the threshold model and the conceptual and operational exclusion of the biphasic dose response; (2) the failure of scientific leaders and government decision-makers to properly understand the hormesis concept and its potential significance; and (3) in the competition of some research ideas hormesis was clearly outcompeted with priorities directed elsewhere.

Hormesis and the failure of scientific leadership

One reason why the medical establishment of the 1930s was highly successful in marginalizing hormesis within the scientific community was due to a virtual lack of engagement on this dose–response issue by researchers whose papers demonstrated evidence of hormetic-like biphasic dose responses in the biological and biomedical communities. This idea will be examined by considering the professional activities of leading hormesis researchers of that era in the years following their initial research supporting the hormesis concept.

- **Ferdinand Hueppe** became a “co-discoverer” of the hormesis concept (calling it Hueppe’s Law) in 1889, writing about it until 1896 in his leading bacteriological text (i.e., *Principles of Bacteriology*). However, he subsequently redirected his career from bacteriological concerns to broader public health issues, relating to community health, including exercise and athletic functions, becoming an official at the first Olympics in 1896. The concept of hormesis only shows up in the later writings of Hueppe (1923) as part of an autobiographical narrative.
- **Hemming Gerhard Jensen** published a well designed and comprehensive dissertation in 1906 at the University of Chicago supportive of hormesis on the effects of several inorganics, including toxic agents such as lead on wheat, yet never published another scientific article in this area. The dissertation was published in the journal *Botanical Gazette* in 1907 (Jensen 1907).
- **Burton Edward Livingston** was a plant physiologist of considerable distinction, receiving his Ph.D. from the University of Chicago in 1901 and eventually became a professor of botany/plant physiology at The Johns Hopkins University with intermediary positions within the US Department of Agriculture and the Carnegie Institute in Washington (Shull 1948). In 1905 he published a detailed study concerning chemical stimulation in algae, a paper that was very supportive of the hormetic dose response concept (Livingston 1905). While it is not known why Livingston initiated this investigation it may be relevant that his advisor at the University of Chicago, Charles Reid Barnes, had collaborative research activities with F.D. Heald and Rodney True, both of whom completed dissertations with Pfeffer in Leipzig, a strong supporter of the hormesis concept as we shall see later (Bunning 1989). In a clarifying autobiographic statement Livingston indicated that toward the end of his appointment at the University of Chicago he spent several months at the New York Botanical Garden conducting an experimental study on the effects of various inorganic salts on green algae (i.e., the subject of his 1905 paper). During this period he became acquainted with Herbert M. Richards and Daniel MacDougal, both of whom studied with Pfeffer (Livingston and Lawrence 1948). The work was remarkably similar to that of Richards and it is possible that this may be where the idea for his research was generated. Despite his significant research findings Livingston soon became interested in the role of diffusion and osmotic pressure in plants, never returning to the hormesis research area with the exception of his graduate student Coggeshall (1931) whose dissertation was a detailed study of the effects of overcompensation stimulation hormesis in the lupine plant following

- exposure to four different toxic chemicals over an broad concentration range with up to 35 different treatments.
- **Charles Richet** who received the Nobel Prize in Biology and Medicine (1913) for the discovery of anaphylaxis, reported the occurrence of hormetic-like biphasic dose responses with respect to the process of fermentation (Richet 1905, 1906–1907). However, he directed his subsequent research activities to areas other than the hormetic dose response.
 - **Charles O. Townsend** was one of the first researchers to report on the phenomenon of over compensation stimulation while completing his dissertation with Pfeffer (Townsend 1899a, b; Bunning 1989). He was to later join the US Department of Agriculture and became the co-discoverer, along with Erwin Smith, of the Crown Gall, the so-called plant tumor (Smith and Townsend 1907). After his initial work on hormesis, Townsend never returned to this topic.
 - **Sarah Branham** an assistant professor at the University of Rochester, Rochester, New York, published a detailed and expanded confirmation of the original work of Hugo Schulz (Branham 1929). However, she soon then left the University of Rochester and future work on the hormesis concept to focus on efforts by the US government to determine the causes and potential cures for meningitis that had recently entered the US from China. During this process she would discover a highly successful treatment for this disease becoming internationally famous (Rees 2008).
 - **Louis Kahlenberg** a long time professor at the University of Wisconsin, reported on hormetic dose responses in plants during a series of experiments assessing the effects of highly dilute solutions as an application of the concept of molecular electrolytic dissociation (Kahlenberg and True 1896a, b). However, Kahlenberg, well known for his high intellect and confrontational nature, entered into a highly technical and prolonged public dispute with his former Ph.D. advisor, Wilhelm Ostwald, Noble Laureate in chemistry (1909) (Kahlenberg 1910). This became a celebrated debate leading to Kahlenberg re-directing his efforts away from the hormesis concept to the “larger” battles of the day (Servos 1996). Nonetheless, Kahlenberg’s research efforts lead to continuing efforts of former colleagues, including Rodney True who later moved to the US Department of Agriculture (USDA) where others were to embrace to some extent the hormesis concept over several decades [e.g., Schreiner and Reed (1908), Humphrey and Fleming (1915), Bateman (1933)] but never in a highly visible, consistent and prolonged manner. Rodney True also became redirected in his research at the USDA toward discovering the causes of plant pathogens on commercially valuable crops (True 1900, 1903, 1905). Edwin Copeland also co-published with Kahlenberg (Copeland 1903; Copeland and Kahlenberg 1899) on the concept of hormesis but he too became redirected to other educational and research issues, including the establishment of an agricultural college in the Philippines, not returning to the topic of hormesis (Wagner 1964). It is noteworthy that True and Copeland received their Ph.D. under Pfeffer at Leipzig (Bunning 1989) studying plant physiology while Kahlenberg was obtaining his Ph.D. under Ostwald in physical chemistry also at Leipzig during the same time period (Servos 1996). Besides location and timing, what brought them together was the belief that problems of other disciplines, especially physiology and toxicology, might be more successfully studied from a physical-chemical perspective, as they did in studies assessing the impact of electrolyte dissolution on the toxicity of dissolved salts on bacteria and plants (Calabrese and Baldwin 2000a, b, c, d, e). The collaboration was also inspired by the fact that Pfeffer’s research on osmotic pressure in plants significantly aided Van’t Hoff (Nobel Prize, 1906) in developing physical-chemical laws for dilute solutions (Servos 1996; Van’t Hoff 1901).
 - **Charles Edward Winslow** was a long time Yale University bacteriology professor, who directed numerous Ph.D. students concerning biphasic dose responses to toxic inorganic agents (Falk 1923). He became oriented to broader public health policy questions in the early 1930s, expanding his focus from that of bacteriology to public health, becoming editor of the *American Journal of Public Health* (1944–1954) (Emerson et al. 1957). Winslow was a major force within the academic and scientific communities but directed these leadership efforts towards broader public health questions, without incorporating the hormesis concept during this period.
 - **Margaret Hotchkiss** was one of Winslow’s Ph.D. students whose research was enormously relevant to the concept of hormesis (Falk 1923; Hotchkiss 1922, 1923). While she had a varied academic career she never returned to the subject of her dissertation, retiring from the University of Louisville in 1962.
 - **Charles Lipman** had an extensive research career concerning the biphasic dose response of heavy metals on plant growth (Lipman and Wilson 1913). In fact, Lipman presented the first “hormesis” data at a major regulatory hearing in 1915 concerning the effects of soil contamination from a large smelter facility in California (Calabrese 2008a; Holmes et al. 1915). Lipman later became redirected toward other questions such as possible bacterial life on meteors (Burke 1937; Lipman 1931, 1932, 1934; Martin 1933), the concept of extraterrestrial life and administrative duties as a Dean at the University of California at Berkeley.

- **Herbert Maule Richards** was a professor of botany at Bernard College of Columbia University. He received his Ph.D. from Harvard University and later studied with Pfeffer in Leipzig (Bunning 1989). Richards published several articles in the last decade of the nineteenth century strongly supportive of the hormesis concept (Richard 1897, 1899). In fact, in his 1899 paper Richards referred to the low dose stimulation as an example of “physiological counter-reaction”, a description similar in meaning to the current overcompensation stimulation definition. He also continued to direct the research of numerous students [e.g., Stehle (1932), Colley (1931a, b), Schelling (1925), Oldenbusch (1922), Latham (1905, 1909), Silberberg (1909), Watterson (1904)] supportive of the hormesis concept until his death in 1928. In 1910 Richards published an extensive summary of these understandings of low dose chemical stimulation in the journal *Science* based on a presentation at a recent AAAS conference (Richards 1910). Richards, along with Benjamin Duggar and Charles Edward Winslow, had the longest and most consistent research focus on the topic of hormesis.
- **Charles Albert Shull** was an extremely productive and accomplished plant physiologist at the University of Chicago, as well as the editor-in-chief of journal *Plant Physiology* from its inception in 1925 to 1945. Based on a grant from the Rockefeller Foundation, Shull and his colleague John W. Mitchell published a detailed experimental report in 1933 indicating that low doses of X-rays stimulate the growth of multiple plant species (Shull and Mitchell 1933). While Shull would have been in a position to promote the furtherance of this research direction, especially with his positive findings, he directed no further research in this area. However, Shull encouraged a former Ph.D. student, Edna Louise Johnson, to assess the effects of low doses of radiation on plant growth (Johnson 1936). One important observation was the confirmation of the initial report of an adaptive response in radiation (Ancel and Lallemand 1928) in which a prior low dose of radiation protected plants against a subsequent damaging higher dose, the significance of which was not appreciated at the time as well as its biphasic dose–response features and capacity for generalizability to other biological systems and endpoints. Despite her confirmation of the adaptive response concept Johnson was not a supporter of the hormesis hypothesis, playing a role in the decision of the NAS Committee to marginalize the hormesis hypothesis concept. The problem that Johnson (1936) had with hormesis was conceptual; she felt that it is was wrong to conclude that accelerated growth following an initial toxic response (i.e. overcompensation stimulation) was an example of “true” stimulation even though this phenomenon was commonly reported. Johnson’s lack of support for the hormetic perspective was a significant factor affecting the acceptance of the hormesis concept since her paper was one of the first major reviews on this topic and along with its occurrence within the very prestigious setting of a major NAS publication, casting it with considerable authority.
- **Edwin B. Fred** was a bacteriologist who made significant contributions to the area of nitrogen fixation. He also contributed significantly to the development of the field of bacteriology by helping to create the *Journal of Bacteriology*, and becoming president of the Bacteriological Society of America. In his dissertation research at the University of Goettington he was introduced to the hormesis concept as his thesis concerned the effects of small amounts of toxic chemicals on the metabolism of bacteria and higher plants. In fact, the concluding sentences of that dissertation state

“The results of this dissertation are therefore that the increased growth of plants after the addition of poisons to the soil is due to a stimulation effect on the lower organisms [the nitrogen-fixing bacteria]. These investigations thus confirm the old physiological law that substances which in higher quantities are poisonous to living organisms, can stimulate the same organisms if administered at low concentrations, and can thus cause increased manifestations of life” (Johnson 1974).

He later published several articles supportive of the hormetic dose response with nitrogen fixing bacteria (Fred 1916) and separate experiments with plants (Fred 1912). Despite his strong orientation toward the hormetic concept he would find himself more interested in the advancing US science with a leadership role in academia, as Fred became the Dean of the Graduate School, Dean of the College of Agriculture and then President of the University of Wisconsin for a combined 24 years (1934–1958) (Baldwin 1985).
- **Benjamin Duggar** first became oriented to the concept of a compensatory stimulatory response following injury while studying in Germany in the late 1890s under the plant physiologist Wilhelm Pfeffer (Bunning 1989). Based on this research, he later published a detailed assessment on the effects of numerous toxic agents on fungal spore germination, noting the common occurrence of a low dose stimulation (Duggar 1901). In fact, that low doses of stressor agents could stimulate growth was a consistent theme in his professional life as was repeatedly acknowledged in research concerning low dose stimulation of fungi and plants by chemicals and radiation throughout the first four decades of the twentieth century. In addition to his own research, he directed and encouraged numerous graduate students and colleagues

[e.g., Kellerman (1903), Reed (1907), Merrill (1915), Schmitz (1924); Smith (1935a, b), (Duggar and Hollaender 1938)] to research in this area during his academic appointments at Cornell University, Washington University/Missouri Botanical Gardens and the University of Wisconsin. Schmitz (1924), who worked with Duggar at the Missouri Botanical Gardens, published extensively on chemicals that could affect the capacity of fungi to decay wood. In this research he demonstrated that a number of agents induced hormetic-biphasic dose response relationships. In fact, it was the research of Schmitz at the University of Idaho that stimulated the later work of Southam and Ehrlich at that institution which eventually lead to their naming this dose–response phenomenon hormesis. As will be noted later Schmitz had considerable academic success, eventually being President of the University of Washington. In the case of Smith at the University of Wisconsin, Duggar proposed the topic of her dissertation (completed in 1934), a topic that demonstrated strong support for the hormesis concept. Yet she did no further research on this topic. Another of Duggar students, Howard S. Reed, became a researcher in the USDA, publishing several articles on hormesis (Schreiner and Reed 1907, 1908). Alexander Hollaender had a particularly noteworthy career and is found below. After his academic retirement in 1943 Duggar would be inspired to “copy” the success of Wakesman and Schatz, the co-discoverers of Streptomycin, the first effective treatment against tuberculosis, making the seminal discovery of aureomycin (Duggar 1948), the first broad spectrum antibiotic, also leaving the concept of hormesis behind.

- **Alexander Hollaender** became the Director of the Biological Division of Oak Ridge National Laboratories in 1945 and went on to become a prominent national and international leader in the assessment of radiation mutagenesis (von Borstel and Steinberg 1996). However, prior to taking this position Hollaender, a radiation biologist, worked closely with Benjamin Duggar at the University of Wisconsin. In 1938 Duggar and Hollaender (1938) reported that low doses of UV radiation provides a growth stimulatory response to bacteria. While this could have lead to important follow up research, Hollaender soon became redirected to assess the potential mutagenic effects of UV, being one of first scientists to theorize that the genetic material was comprised of nucleic acids rather than protein (Hollaender and Emmons 1941). Nonetheless, the prodigious leadership skills of Hollaender were directed to the nescient field of radiation mutagenesis rather than hormesis.
- **George Sperti and John R. Loofbourow** were active researchers from the mid 1930s to the late 1940s consistently reporting that yeast cells injured by UV radiation produced a substance(s), which enhanced growth when added to non-irradiated suspensions of yeast or to cultures of various bacterial strains and mammalian cells (Heitmann 2002; Loofbourow et al. 1938; Sperti et al. 1937). The biphasic nature of this growth stimulatory response was consistent with the quantitative features of the hormetic dose response (Loofbourow and Morgan 1940). This research obtained considerable prominence with multiple publications in *Nature*, *Science* and other leading journals. These researchers closely linked their findings with fundamental wound healing processes and with the process of tumorigenesis. However, several factors intervened which lead to the failure of this concept to thrive (Heitmann 2002). Their research was intellectually guided by the Warburg cancer hypothesis that was severely criticized in 1943 by Stern and Wilhelm (1943). The Sperti/Loofbourow group failed to challenge this criticism at a critical juncture of the scientific debate, redirecting research from more theoretical research to practical applications including commercial products. World War II challenges redirected the research of Loofbourow, then at MIT, toward military applications of his research with UV. Finally, Loofbourow died unexpectedly in 1951 at the age of 48 (Anonymous 1951).
- **Henry Welch** was a high level USFDA official, who demonstrated the hormesis concept in significant experimental microbiological studies in the mid to late 1940s. His research suggested that low doses of penicillin and streptomycin stimulated bacterial colony growth enhancing mortality in animal models (Welch et al. 1946; Randall et al. 1947). While this could have created an opportunity for a detailed assessment of the hormesis concept and its public health/medical implications, Welch was forced to resign his appointment because of financial conflict of interests due to ownership of private sector publications (Anonymous 1960a, b), leaving the hormesis idea without its advocate within his agency.
- **John Ehrlich** along with Chester Southam, gave the scientific community the term hormesis in 1943, based on their research with chemically induced fungal metabolism (Southam and Ehrlich 1943). Soon after their seminal hormesis paper Ehrlich left the University of Idaho, going to the University of Minnesota to work on a project to enhance the synthesis of penicillin during World War II (Vaughn 1950). Ehrlich later moved to the Parke-Davis pharmaceutical company in Detroit, Michigan, and became the co-discoverer of the antibiotic chloramphenicol (Ehrlich et al. 1948), again never returning to the hormesis concept.
- **Chester Southam** studied the concept of hormesis for his undergraduate and MS theses at the University of Idaho. Along with his advisor, John Ehrlich, they created the term hormesis, as first seen in his 1941 unpublished

undergraduate thesis and later in his 1943 publication with Ehrlich. After completing his MS degree in forestry he left Idaho to attend Columbia University medical school in New York City. He became a world renowned scientist concerning tumor antigens, never returning to the concept of hormesis (Southam 1967a, b). He also was involved in a major scandal in which elderly subjects were injected with human cancer cells without their informed consent (Lerner 2004; Preminger 2002). While Dr. Southam had his license to practice medicine revoked for 1 year, he was able to effectively rehabilitate his professional reputation, later becoming president of the American Association for Research on Cancer. He died in 2002 (Anonymous 2002).

US Federal agencies and hormesis

While regulatory agencies are groping currently with how to integrate hormetic dose responses into the risk assessment process, the US Department of Agriculture (USDA) has had a long and continuing interest in and recognition of hormetic dose response relationships. The listing of early well known USDA investigators such as Rodney True, Charles O. Townsend, F. D. Heald, Horris Reed, and Ernest Bateman all published studies demonstrating hormetic dose responses. In a 1915 USDA publication Humphrey and Fleming (1915) explicitly emphasized that very dilute concentrations of toxic wood preservatives ordinarily produce a stimulatory effect of fungal growth while being inhibitory at higher concentrations. Nearly two decades later Bateman (1933) in another USDA publication provided a detailed review of some of the earlier plant related hormesis literature, indicating the need to include an assessment of stimulatory effects of low doses of toxic agents in any general toxicological assessment. The interest of the USDA in the theoretical and practical aspects of hormesis continues to the present as seen in the research on herbicides such as glyphosate (Duke and Powles 2008). As noted in the brief summary of Henry Welch, FDA researchers published several papers on the capacity of low doses of antibiotics to enhance microbial proliferation and thereby lead to the deaths of mice (Welch et al. 1946; Randall et al. 1947). These researchers used the term hormesis to describe their biphasic dose response relationships. However, when Welch was forced to step down from his position the interest in hormesis within this organization diminished.

Placing early hormesis researchers in perspective

An assessment of the careers of nearly 30 researchers reporting significant supportive studies on the hormesis

concept during the early decades of the twentieth century revealed that there was no apparent general consolidation of biological thinking on the nature of the dose response. The research developments that did occur seemed academically isolated, with reports in areas relating principally to yeast metabolism and colony growth, bacterial colony growth, fungal spore germination, plant growth stimulation, wood rotting prevention research with more limited research directed toward insect longevity (Davey 1919). There was little or no effort made to integrate these divergent areas of research into a general dose response theory. It is true that Duggar directed considerable attention to the occurrence of hormetic-like dose response in his plant physiology textbook (Duggar 1911), that Falk (1923) strongly emphasized the significance of Hotchkiss's (1922) hormetic findings with bacteria and several bacteriological texts from the 1930s onward indicated the low dose stimulation (Salle 1939). Discoveries of plant auxins in the 1930s began a major redirection in plant physiology continuing throughout the remainder of the 20th century. However, the dose response relationship for such auxins was again strikingly biphasic with quantitative features fully consistent with the hormetic dose response (Thimann 1937), yet, authors of that era generally failed to integrate the earlier findings with non-essential toxic substances summarized by Duggar (1911) with new physiological developments. In fact, this lack of integration may well have been intentional. Symbolic of this overall failure to embrace the hormetic dose response concept is seen with Richards (1910) who gave a major presentation at the AAAS conference on hormesis-related chemical stimulation followed by a 12 page paper based on this topic in the journal *Science* and yet it was cited but once in 98 years, until the present paper.

By the early 1940s the hormesis concept had already become severely tainted within the scientific community. With respect to low doses of non-essential agents stimulating plant growth, Sellei et al. (1942) stated that “scientists in general are loath to admit the effectiveness of such extraneous substances, unless very extensive experiments have been carried out...” Investigators however, who observed hormetic-like biphasic dose response with toxic and otherwise non-essential agents were “hesitant about getting connected with a field which seemed to be in very low repute among biologists” (Sellei et al. 1942).

Underlying the failure to integrate the extensive, yet isolated disciplinary findings on the biphasic nature of the dose response is that the hormesis oriented researchers of that era generally became professionally redirected to any of a wide range of activities, in effect leaving the hormesis concept behind without programmatic continuity. Several researchers, such as Fred, Heald, and Schmitz became highly involved with University administration developing

programs to support academic research, with Fred and Schmitz becoming the president of the Universities of Wisconsin and Washington, respectively. Several others such as Winslow and Shull were longtime editors-in-chief of major journals (*Journal of Bacteriology* and the *American Journal of Public Health*, Winslow; *Plant Physiology*, Shull), diverting much of their time to general editorial activities. In contrast, Richards was devoted to directing undergraduate research at Barnard College, a prestigious women's undergraduate college. Approximately ten articles were published on the hormesis concept, all only under the name of the student. While the research was of good quality it did not lead to any of these students taking the concept forward as it might be expected for a graduate student. Furthermore, the papers (except for one) were published in a classical botanical journal (*Bulletin of the Torrey Botanical Club*, changed to *Journal of the Torrey Botanical Society* in 1998) which is not cited in major toxicological indexes such as PubMed, Web of Science, or BioAbstracts, making it difficult to discover these papers. In fact, the early indexing for botanical (1918–1925) (Schramm 1919) and bacterial (1917–1925) articles started independently, to be later integrated into Biological Abstracts in 1926 (Parkins 1966), all after the initial set of publications on hormesis. None of the Richards papers, even those published after 1926, were present in the abstracting publications. Other scientists such as Branham got redirected to important public health issues as she became focused on the causes and cures of meningitis, while Hueppe was redirected toward nationalistic cultural developments in Germany and Lipman became interested in the possibility of extraterrestrial life, all leaving the hormesis concept behind. Some others died unexpectedly as in the case of Loofborow or simply never published beyond their dissertation as in the case of Jensen. True was initially a vagabond scientist, simply trying to find a stable position. Once he did find such a position at the USDA he developed research collaborations with scientists within his agency and with scientists at academic institutions (True and Oglevee 1905; True and Gies 1903). However, bureaucratic challenges overtook True's hormetic interests and he also drifted away from the hormesis topic.

The most consistent intellectual leadership directing graduate level research concerning the hormetic concept in the early decades of the twentieth century was that of Winslow and Duggar, but their interests were very broad as each was often involved with significant national leadership roles within various aspects of the scientific community which tended to crowd out their research focus, as this was especially the case for Winslow. In the end, the research community never coalesced around the issue of the hormetic dose response, lacking leadership, focus, continuity, and a sense that the topic had broad overriding and general-

ized significance. It is also important to note that none of these researchers were noticeably drawn into debates over homeopathy and Schulz's dose response theories. All seemed to be particularly drawn to see the issues principally as scientific questions. It appears that none were involved in the dose response battle between traditional medicine and homeopathy and it was never highlighted in their papers. However, by the time this first generation of hormesis-oriented researchers had drawn to a close, their basic findings were essentially dismissed as seen within the striking comments of Sellei et al. (1942).

Willhem Pfeffer, the principal inspiration of hormesis research in the US

The internationally famous German scientist Willhem Pfeffer (1845–1920) supported the findings of Schulz concerning the stimulatory effects of low doses of chemical disinfectants on yeast metabolism (Pfeffer 1901). Pfeffer, along with Julius Sachs (1832–1897), is considered the father of modern plant physiology. Of particular importance to the hormesis story is that several hundred scientists from European countries, Japan and the US flocked to Pfeffer's laboratory for education and training during the 1890s and first decade of the twentieth century. In this context, a number of key scientists in the early decades of the twentieth century who conducted plant and fungal related hormesis research in the US have their research direction traced directly back to their experience with Pfeffer (Bunning 1989). These scientists included Edwin Copeland, Rodney True, Charles Townsend and Daniel McDougal who completed dissertations under the direction of Pfeffer. In the case of McDougal, all his Ph.D. research was undertaken with Pfeffer but his degree was awarded at Purdue University in the US (Moore 1939). Herbert M. Richards published several papers concerning hormesis based on this research with Pfeffer (Bunning 1989). Similar experiences were found to have occurred for Benjamin Duggar (1901) and Ernest Heald (1896) (Bunning 1989). Each of these individuals returned to the US and continued to publish papers supportive of the hormesis concept, influencing other colleagues, students and research organizations (e.g. USDA) as noted above. Somewhat tangential, but also connected to the Pfeffer research perspective, was the experience of Charles Lipman at the University of California, who was mentored in his early academic years in California by Jacques Loeb who himself was strongly influenced by Julius Sachs, the professor mentor of Pfeffer (Bunning 1989).

While there were other researchers in the US that independently assessed hormetic research hypotheses (e.g., Winslow), the impact of Pfeffer is both unique and extensive, yet not previously explored in the historical context of

hormesis. In fact, the available information suggests that the person having the greatest overall impact on the occurrence of hormesis related research in the US during the first three decades of the twentieth century was Pfeffer via his returning students. Further, the original and sustaining focus of Pfeffer to the issue of low dose chemical stimulation was clearly scientific, with no linkage to the debate between traditional medicine and homeopathy. This may be why the research on hormesis in the early decades of the twentieth century in the US follows the non-ideologic course set by Pfeffer, also contributing to some extent to its general lack of overall programmatic-like direction but rather individual investigator initiatives. It is of interest to note that none of the returning US scientists ever co-authored a paper with another US scientist from the Pfeffer laboratory on the hormesis topic, although a number of these scientists did become associated with the USDA for different periods of time and had other important professional associations (e.g., creating Biological Abstracts). A further factor affecting the lack of cohesion around the topic of hormesis was the perspective that the returning Pfeffer students were to become important national leaders in the development of the field of botany and plant physiology. Major goals were structural, that is, creating academic programs, new facility positions, graduate programs, new facilities, new journals and even the abstracting services (such as Biological Abstracts). These activities directed some Pfeffer graduates into major leadership roles, while drawing them away from a cogent and integrated focus on the nature of the dose response in the low dose zone. This framework serves to clarify, at least in part, the reason for the lack of interest in challenging the institutional-like dose–response fiat of Clark which led to the demise of the hormesis concept and the elevation of the threshold model as the default model for regulatory purposes.

Concept competition

In addition to lack of scientific leadership, there were scientific and societal conditions that place very high priority on some topical areas and far less on others. The concept of hormesis was seen losing out to several other ideas, further accelerating the conditions for concept marginalization.

Antibiotic induced resistance versus antibiotic induced hormesis

The concept of hormesis preceded that of antibiotic resistance within the microbiology/bacteriology literature. In fact, the concept of hormesis was widely recognized in mainstream bacteriological research from the early 1920s with

particular research emphasis on toxic inorganics (Falk 1923; Hotchkiss 1922, 1923). It was also discussed prominently in textbooks (Salle 1939; Clifton 1957; Lamanna and Mallette 1965) and journals (Marshall and Hrenoff 1937). By 1942 the concept of bacterial resistance to antibiotics was first published (Rammelkamp and Maxon 1942) and by the end of the decade became viewed as a major scientific, medical and public health issue. For example, in his 1949 report Dunlop (1949) reported that resistance assumed widespread and practical importance in the interaction of sulfonamides and the treatment of gonococcus. This organism was quickly and highly refractory, with the percentage of treatment failures exceeding 85%. On the other hand, the concept of hormesis was experimentally based on animal model findings (Welch et al. 1946; Randall et al. 1947) with little evidence related to clinical application (Garrod 1951). While low doses of several widely used antibiotics were experimentally shown to enhance the lethality of harmful bacteria presumably via increasing colony proliferation in mice, these findings never created a broad interest as well as generating significant public health concerns (Welch et al. 1946; Randall et al. 1947). The two key papers that noted the hormesis-enhanced antibiotic induced mortality in mice have been cited a collective total of only 30 times since their publication in the 1940s whereas the first ever publication of antibiotic resistance has been cited 165 times. Even this large disparity profoundly understates the significant impact that antibiotic resistance has had on research in the scientific community with numerous follow-up publications, as well as public health and medical practices as compared to the hormesis concept. Thus, one reason why the hormesis concept failed to develop and thrive in the biological and medical sciences is that it was profoundly outcompeted by a complementary concept that was easily and broadly understood and deemed to be of extraordinary importance. That is, the hormetic findings had harmful implications but it was shown only in mice, whereas marked resistance was strikingly demonstrated in people. Without question, the resistance issue became predominant, completely masking the hormesis concept to researchers, the public, and policy makers. This may be seen within the context of the public having experienced the substantial significance of antibiotics in the treatment of numerous life threatening diseases such as tuberculosis and pneumonia in their own lives, as well as in the treatment of venereal disease, and their concern that bacterial resistance may affect a return of these diseases or their lack of effective treatment. Thus, the resistance concept took central stage, leaving the hormesis concept far behind and quickly forgotten.

Radiation versus antibiotic treatment of disease

During the early decades of the twentieth century radiotherapy was widely used for the treatment of inflammatory conditions,

including the furuncle (boil), carbuncle (suppurating inflammation of the skin and subcutaneous tissues due to *Staphylococci*), pyrogenic (pus) infections, pneumonia, trachoma, parotitis, nephritis, and numerous other inflammatory conditions. With respect to pyrogenic infections, the findings generally indicated that the majority of patients given radiotherapy displayed rapid and substantial clinical improvements, with symptoms often markedly diminished within a day. The radiotherapy was also seen as interrupting the expected progression of the infection, reducing the need for additional treatment. The magnitude of the clinical literature during this period was substantial as in the case of Heidenhain (1926) who reviewed some 855 cases with 76% recovering without the need for surgical intervention. The principal factors related to these clinical successes using X-rays for inflammatory symptoms was the speed of improvement and the generally modest dose of radiation required, that is, doses of 50–150 r were judged as very effective in a large proportion of the cases (Borak 1944).

Similar beneficial effects were also reported in the case of pneumonia. For example, in 1916 the Quimby's verified earlier claims of effective treatment of pneumonia by X-rays (Quimby and Quimby 1916). These authors stated that “no pathologic process in the body responds quicker to an X-ray exposure than the non-resolution following pneumonia”. Their findings were repeatedly confirmed over the next several decades related to postoperative pneumonia and for pneumonia unrelated to surgical intervention (see Calabrese and Baldwin 2000c, Table 2, page 66). In addition, beneficial effects of X-rays have also been widely reported for the eye disease, trachoma, which involves sclerotization of eyelids (see Calabrese and Baldwin 2000c, Table 2, page 66).

Further success was reported in the treatment of patients for gas bacillus infections as well as acute peritonitis. In numerous patients Kelly (Kelly 1936) used doses of 75 r/day for two days with considerable success. Such findings were soon supported by numerous other researchers (Dowdy and Sewell 1941; Merritt et al. 1944; Cantril and Buschke 1944). Before the 1930s the mortality rate for gas gangrene exceeded 50% along with the frequent need for amputations. However, once the use of X-rays was adopted the mortality rate and the need for tissue removal strikingly reduced to about 5% (see Calabrese and Baldwin 2000c, Fig. 5, page 67).

The issue of what is a clinically beneficial dose and how that relates to the concept of hormesis is an important consideration. Several leading research groups indicated that if the dose required to cause skin erythema is assumed to be 100%, the dose successful in treating inflammatory conditions has typically been less than 50% and at times even less than 10% (Borak 1944; Desjardins 1931, 1937, 1939a, b, 1942). Furthermore, they emphasized that the results

obtained with doses approaching the skin erythema dose were usually less successful than those treated following the administration of a lower dose, thereby suggestive of an hormetic dose response.

This summary of the clinical literature of the beneficial effects of X-ray therapy is based on a large number of studies during the initial four decades of the twentieth century. Such studies were frequently conducted at prestigious medical institutions in Europe and the US, and being published in leading journals. The clinical research was also supported by animal model research using more rigid experimental study designs, placing conclusions on a firmer causal basis (Glenn 1946a, b). The mechanisms by which the treatments reduced disease severity was highly debated but thought to involve activation of immune processes consistent with the hormetic dose response perspective.

While these radiation treatments had a marked impact on clinical practices, this quickly faded with the introduction of several key antibiotics from the mid 1940s to the early 1950s along with mounting fears associated radiation induced cancer due to the atomic blast during World War II. The potential clinical benefits of radiation in the treatment of the above diseases were soon forgotten. The failure of this type of radiation therapy to compete in the treatment marketplace also represented a failure of the hormesis concept within the medical community and the general public. While the weight of evidence supported a causal relationship of the X-ray treatment and the wide range of clinical improvements, the issue of whether the response was actually consistent with the hormetic dose response hypothesis is difficult to resolve within the framework of epidemiological studies as they often did not include a broad range of doses. Nonetheless, in the case of the therapeutic use of X-rays to treat a wide range of inflammatory diseases, it appears fairly conclusive that there is a low dose benefit, high dose toxicity, thus displaying consistency with the hormesis concept.

Societal concerns with toxicity rather than benefit, that is, the hormesis concept wasn't relevant

During twentieth century there was a strong interest in preventing toxicity to workers. This is evident in the establishment of worker exposure standards starting in the 1930s by various states and the creation of the American Conference of Governmental Industrial Hygienists (ACGIH) in 1938 that provided recommended exposure standards to industry until they were fully adopted as governmental standards in 1970 with the creation of federal legislation (Calabrese 1978). Similar activities were also occurring with respect to environmental health standards with community based

exposure standards being established for contaminants in drinking water, ambient air and later for soils. The prevailing perspective of the regulatory and public health agencies was to prevent toxicant induced harm by lowering exposures as much as possible below federal standards under the belief that lower is always better. There was no formal consideration given to the possibility that the risk assessment models for carcinogens and non-carcinogens might provide fundamentally incorrect risk estimates in the low dose zone. There is no evidence that serious consideration was given to the possibility that low doses of harmful agents might induce potentially beneficial responses in experimental and population-based settings. There was also no understanding that responses below the threshold might also be toxic depending on the specific circumstances. However, in 1976 Luckey noted that forthcoming environmental legislation should take the concept of hormesis into account, advice that was obviously not followed.

Hormetic Growth Stimulation vs Mutation

In the 1920s and 1930s low doses of radiation were widely reported to cause a growth/cell proliferation response in microorganisms, including algae, fungi and yeast (Calabrese and Baldwin 2000a, b, c, d, e). During this same period there was considerable interest in the findings of Muller (1927) and Stadler (1928) that X-rays could cause mutations in insects and plants, respectively. The mutation concept and discovery was a profound development, with Muller receiving the Nobel Prize in 1946. It led the US National Academy of Sciences to create a long-term study of radiation and its biological effects, including mutation starting in 1929 (Curtis 1929) and into the 1930s (Duggar 1935, 1938). One of the leaders in this National Academy activity was Benjamin Duggar, who transformed his laboratory at the University of Wisconsin to study radiation effects (see Elizebeth C. Smith above), involving Alexander Hollaender. In their initial studies Duggar and Hollaender (1938) reported a low dose stimulatory effect on microorganism growth/proliferation. Follow up work by Hollaender and Emmons (1941) with fungi, under the guidance of Duggar, revealed that the radiation induced fungal mutants were due to alterations in nucleic acid composition, thus becoming one of the first groups to propose that the gene was not made of protein but nuclei acid. Although Hollaender's idea was far ahead of field at the time, and not widely accepted, it inspired him to focus on the concept of mutation and its theoretical and public health implications. For Hollaender the decision between research on the hormesis growth concept or on the mutation/nucleic acid area, the choice was easy as history shows. However, it should be pointed out that hormetic effects have now been widely

reported in the mutagenicity literature (Maki-Paakkanen and Hakulinen 2008; Wilms et al. 2008; Demisia et al. 2007; Lacoste et al. 2006; Pu et al. 2006; Jagetia et al. 2003; Knasmuller et al. 2002; Sasaki et al. 2002; Hartmann et al. 2001; Kirkland and Muller 2000).

Concept application failure

The USDA sponsored a 22 research center location study to evaluate the capacity of low doses of three radionuclides to stimulate growth in 20 plant species in the late 1940s, based on considerable earlier research (Calabrese and Baldwin 2000c) indicating interest in a possible practical application of the hormesis concept. While “proof of concept” seemed well established based on prior research, “proof of application” was a further challenge. However, this massive study was poorly designed as there were no prior dose ranging studies conducted, all plant species were administered the same dose, with only one dose used. In fact, it is hard to imagine a more poorly designed investigation concerning an assessment of possible hormetic effects (Alexander 1950). This extensive study failed to “prove” the applicability of hormesis thereby dampening enthusiasm for the hormesis concept, further marginalizing the concept within the federal funding agency network and the scientific community. The timing of this failure was particularly significant since it occurred as the US federal government was establishing a national radiation research program. Thus, leading researchers were not encouraged to explore the hormesis area nor would low dose stimulatory hypotheses receive funding priority. The occurrence of such practices was evident within program activities of the Radiation Research Society during the 1950s and 1960s as this topic never surfaced during the national meetings.

Failure to understand the hormesis concept by scientific and governmental leaders

A significant factor affecting the recognition and acceptance of hormesis was a lack of consensus, and, possibly frank confusion as to what it was. Key to this issue was whether the observed stimulation was of a direct or compensatory nature. In fact, one highly influential intellectual encampment within the radiation biology field held the view that hormesis did not exist because the stimulatory responses they observed, though reproducible, were the result of a modest overcompensation following radiation induced injury and not a “true” stimulation (Holzknecht and Pordes in Gordon 1930). In contrast, other similarly prominent individuals, such as Fraenkel (Gordon 1930) argued that small doses of radiation stimulated by a direct

biopositive effect. This confusion over whether the low dose stimulatory response of the Arndt-Schulz Law was a direct or only in response to induced damage emerged as an important issue that was a highly contentious issue starting in the 1920s.

Lack of agreement of this concept continued unresolved into the late 1930s to early 1940s. For example, the highly prestigious Harvard professor and first Director of the Division of Biology and Medicine at the US Atomic Energy Commission, Shields Warren, strongly promoted the Holzknecht and Pordes perspective by his statement that the assumption that small doses of radiation are directly stimulatory is false and that the Arndt-Schulz Law (i.e., hormesis) is therefore invalid. He stated further that the slight stimulatory activities (i.e., modest overcompensation stimulation) offered as evidence of this concept are in fact only reparative response to the injury (Warren 1945). Thus, the rejections of the hormesis concept by prominent scientists such as Edna Johnson, a funded University of Colorado researcher of National Research Council (NRC) and significant contributor to their scientific and policy perspectives on the radiation hormesis concept and public leaders such as Shields Warren and other researchers (Greenfield 1937) over the observation that the stimulatory response was “only” a response to damage and not a true direct stimulatory response may well have been the key critical judgment that led to the marginalizing of the hormesis concept.

In light of this determining judgment, it is ironic that over 60 years later that the definition of hormesis that is most widely discussed is that of a modest overcompensation to a disruption in homeostasis (Calabrese and Baldwin 2002). It is ironic still further to note that this is the concept that was recognized as being most consistent with the available data even during the 1930s and 1940s (Calabrese 2001). In fact, the replication and generalization of the original Schulz findings by Branham in 1929 thoroughly documented the overcompensation stimulation phenomenon. Thus, in retrospect Warren and other leaders who rejected the hormesis concept at that time had developed a correct scientific understanding of overcompensation stimulation, but they marginalized its role to the point of biological trivialization. As subsequent documentation would confirm, both direct and overcompensation stimulation commonly occur and the quantitative features of different manifestations of the hormetic dose response are similar (Calabrese et al. 1999). In fact, Smith (1934, 1935a, b—dissertation and journal papers, respectively), the student of Duggar, demonstrated both radiation induced overcompensation (i.e., fungal growth) and direct stimulation (i.e., fungal spore production) in her dissertation research, a finding that was somehow missed by Johnson (1936) in her assessment for the NAS as well as Shields Warren.

Hormesis “rediscovered”

The reporting of hormetic-like biphasic dose responses became more evident as the late 1970s approached. A variety of biological and biomedical disciplines independently began to document the hormetic-like dose response with terms that evolved specific to their discipline. The field of epidemiology started to document U-shaped dose responses to various human health conditions, especially those that related alcohol consumption and various parameters of cardiovascular diseases (CVD) (Marmot et al. 1981), with such studies now numbering in the many hundreds, with subject areas expanded far beyond both alcohol and CVD. Genetic toxicology started to document the adaptive response phenomenon in which a low dose of mutagen would protect against damage from a subsequent more massive exposure to the same or different mutagen (Samson and Cairns 1977). This was soon expanded to include the field of radiation, with the adaptive response to ionizing radiation being reported in 1984 (Olivieri et al. 1984). As subsequent studies demonstrated, the adapting doses would display an optima, with the dose response closely following the scheme of the hormetic-biphasic pattern (Schollnberger et al. 2007; Redpath et al. 2003).

The field of pharmacology was provided a conceptual consolidation of hormetic-like biphasic dose responses by Szabadi (1977) who integrated pharmacological examples of biphasic dose responses stretching from those of the Nobel Laureate, Dale (1906), and developed a mechanistic framework within which such responses could be evaluated. Biphasic dose responses were similarly reported in ecological toxicology led by Stebbing (1982). Like the research of Szabadi, Stebbing had proposed a mechanistic framework to evaluate the hormetic dose response. In fact, Stebbing used the term hormesis to describe this phenomenon. In the field of radiation biology Luckey (1980) published a substantial summary of the capacity of ionizing radiation to cause hormetic effects across the broad spectrum of biological models, from microbes to man. By the mid 1980s the concept of “pre-conditioning” had been reported in the biomedical domain (Murry et al. 1986), a phenomenon directly comparable to the adaptive response phenomenon in the area of mutagens and even earlier in chemical toxicology where this phenomenon was called autoprotection although these authors did not present their findings within a dose response context (Ugazio et al. 1972). This convergence of observations and dose response concepts provided the foundation upon which the current assessment of hormetic is occurring, a foundation which is based on a highly diverse and extensive empirical base, yet within a mechanistic framework. The observations of hormetic-biphasic dose responses became accelerated from the mid 1980s onward as a result of marked improvements in

the capacity to measure chemical concentrations at progressively lower levels as well as a result of the profound expansion of cell culture studies and the use of well plates that permitted the testing of large numbers of concentrations in a very cost-effective manner.

Validating the dose–response

During the mid 1970s US regulatory agencies were forced to confront the challenge of determining the shape of the dose response in the low dose zone for chemical carcinogens. This was critical since the 1970s were a period during which extensive environmental legislation in the US was created to address multi-media contamination. Exposure standards had to be set for toxic substances in the water, air, food and eventually in the soil. To address this challenge the US FDA undertook what was called the “mega-mouse” study. This extraordinary investigation, which involved the use of more than 24,000 animals, assessed the responses of the genotoxic carcinogen 2-acetylaminofluene (2-AAF), a known liver and bladder carcinogen in some rodent models. Since the results of this study were likely to have a determining effect on carcinogenic risk assessment practices in the US and worldwide, the US Society of Toxicology created a 14 member independent expert Task Force to perform their own analysis of the data of the original findings (Bruce et al. 1981). The analyses became controversial because the FDA analysis of the data reported an apparent linear dose response for the liver cancer and an apparent threshold for the bladder cancer (Gaylor 1979). However, in the SOT Expert Task Force approach, the methodology incorporated the parameter of time, since intermediate sacrificing had been incorporated into the study design. When a dose-time-response modeling of the data was performed, a different picture of the data emerged than had been observed within the context of a dose–response relationship (Gaylor 1979). In this case, the findings revealed a striking J-shaped dose response for bladder cancer. There was a clear threshold of effect, with the incidence of bladder cancers decreasing below the control values in the below threshold zone. The findings were consistent across the six rooms in which the animals were held, providing a type of built in replication. The authors were very explicit in their depiction of the findings as they emphasized the hormetic-like nature of the dose–response. In the case of the liver cancer, the lifespan of those animals in the lower dosed groups were prolonged beyond that of the control group, an observation again at odds with standard conventional beliefs but consistent with the hormetic perspective. The SOT Task findings were to occupy nearly an entire issue of the SOT journal *Fundamental and Applied Toxicology*. Thus, in the largest rodent cancer bioassay ever conducted,

the hormetic dose response was validated by the analysis published by the SOT Task Force.

Despite the strong support of the hormetic model by the SOT Task Force, the US EPA and FDA adopted linearity at low dose modeling for cancer risk assessment modeling, a decision that has been controversial and in conflict with the data that was designed to guide such governmental judgments. In an even more unusual twist on this matter, several years later the SOT would issue/sell an educational set of slides illustrating toxicological concepts. In their addressing the issue of low dose cancer assessment the SOT ignored their own published SOT Expert Task Force assessment and adopted the government perspective. Such historical background provides a framework that may provide insight on why there has been so much opposition to the hormetic challenge to the current and longstanding dose response paradigm. A current addendum to this story is worth noting. The 2008 version of the leading toxicology textbook, Casarett and Doull’s *Toxicology, the Basic Science of Poisons*, a chapter dealing with dose response used the 2-AAF mega mouse data to illustrate the linearity and threshold dose response models, failed to acknowledge the SOT Expert Task Force analysis with the dose-time-response demonstrating an hormetic response (Eaton and Gilbert 2008).

With the decision to adopt low dose linearity in regulatory agency based risk assessment practices, the chemical and utility industries tried to challenge this perspective by claiming that the most fundamental nature of the dose response was that of a threshold. Thus, for possibly scientific, but also for financial reasons, these industries concluded that the EPA and the FDA were wrong to adopt linearity at low dose modeling for cancer risk assessment. However, since the number of doses in essentially all cancer bioassays is modest it was never possible to prove which model, that is, linear at low doses or threshold, best explained the data. Under such situations, the federal agencies would always revert back to the most conservative, that is, most protective, estimates, thereby rejecting the threshold model, accepting the linearity predictions, which, of course, was also not capable of being validated due to resource limitations. For even the mega-mouse study with its 24,000 animals was only capable of providing risk estimates down to the 1 in 100 risk range, thus this mega-mouse study has long been known as the ED01 study.

Since the threshold model could not be used to challenge successfully the linearity at low dose modeling of the federal regulatory agencies, the next strategy was to explore the possibility that the long marginalized hormetic dose response might be able to accomplish this task. Influenced by the 1980 book of Luckey on radiation hormesis, the electric power industry in Japan and the US worked together to create the first ever conference on Radiation

Hormesis in August, 1985, with the proceedings being published in the journal *Health Physics* in 1987. This activity led to an invited debate on the topic of radiation hormesis in the journal *Science* in 1989 (Sagan 1989; Wolff 1989), renewing interest on the topic. This directly led to the creation of the BELLE Advisory Committee based administratively at the University of Massachusetts at Amherst that created a widely distributed scholarly newsletter (www.belleonline.com) dealing with hormesis and a series of conferences on this topic along with conference proceedings. Eventually these activities lead to the creation of an hormesis database (Calabrese and Baldwin 1977, 2005) that could be used to assess the generalizability of hormesis as well as the frequency of hormesis within the toxicological and pharmacological literature. The findings may have been surprising to many as these data indicated that the hormesis concept was broadly observed, highly generalizable, independent of biological model, endpoints measured and chemical class/stressor agent. In head to head large scale comparisons with the threshold model the hormesis model was far more accurate in predicting responses below the threshold (Calabrese and Baldwin 2003, 2001; Calabrese et al. 2006). In fact, the threshold model performed in a consistently and generally surprisingly and strikingly poor fashion. These findings have led to major textbooks in toxicology now incorporating the concept of hormesis (Eaton and Gilbert 2008; Klaunig and Kamendulis 2008; Beck et al. 2008). Similar efforts to incorporate the concept of hormesis in other biological disciplines is now occurring in the areas of pharmacology (Calabrese 2008p), aging (LeBourg and Rattan 2008), and neurosciences (Calabrese 2008b, c, d, e, f, g, h, i, j, k, l, m, n, o). Strong efforts have also been made to integrate dose response concepts and terminology within an hormetic framework (Calabrese et al. 2008). These developments are reflected in the increase in publications and citations dealing with the hormesis concept with about 90% of such listings occurring since the year 2000.

The ten top reasons why hormesis failed to thrive

The acceptance and societal integration of the threshold dose response model during the early mid decades of the twentieth century was less an abrupt intellectual “take over” of a toxicological or pharmacological throne but rather the end result of a series of “moves”, leading to a progressive weakening of the hormesis biphasic dose response theory and in effect replacing it with threshold dose response model. It wasn’t really an intellectual Coup d’etat since there was no broadly accepted (e.g., reigning) dose response model at that time. The establishment of the threshold dose response as the functional default model for

the scientific and regulatory communities however did not happen by chance, although all such successful operations depend on good luck (i.e., the unique intersection of multiple conditions) and this was also the case here.

First—Clark’s attack. The most significant development in this process was the work of Alfred J. Clark, who consolidated previous criticisms of homeopathy and Schulz, some of which was seriously incorrect, and dressed them in the clothes of modern quantitative pharmacology and distributed these criticisms in prestigious journals and highly regarded textbooks. He also made sure that his views about homeopathy and Schulz were known by his peers, who were scientists of the highest achievement and visibility. Due to the power of his arguments and his elevated status within the scientific community Clark was able to effectively discredit homeopathy and trivialize Schulz, making him both irrelevant and a notable scientific talent who nevertheless made a serious fatal error and making this criticism stick. The talented Clark was also able to offer a credible alternative to the discredited Schulz model, presenting the threshold model with supportive data and confirmed with the powerful statistical features of that era.

Second—Hormesis concept is difficult to prove and biological significance often uncertain: The low dose stimulatory response can be very difficult to prove because the magnitude of response is modest being only 30–60% greater than the control at maximum. Such a modest response can be very difficult to distinguish from control groups, especially if they are inherently highly variable. Unless the study designs are robust, with adequate numbers of properly spaced treatment groups and a commitment to replicate studies hormetic findings are very difficult to confidently distinguish from background noise. Hormesis became very hard to demonstrate after the “establishment” of the threshold model, since this model led to toxicology being a high dose-few doses discipline, characteristics which were further re-enforced by the belief that the hormetic response does not exist.

Third—modeling hormesis out of existence: The next stage of the threshold “takeover” and the demise of the hormesis concept was incorporation of the maximum likelihood estimate method within the Probit model (Bliss 1935b), Fischer 1935-see appendix (Bliss 1935b) which effectively denied biological reality to the hormesis dose response concept. This important modification to the Probit model led to a constraining of the response in the low dose zone to always be above the control value leading to the conclusion that such responses below the controls (i.e., hormetic responses) represent variation and not a real treatment related response. This represented a critical development since it was subsequently adopted by the FDA and EPA in their methods to estimate cancer risks at low doses.

Fourth—Bliss’s publication crusade to establish threshold-based probit model: Bliss soon published numerous versions of the threshold model with Probit applications to various biological sub-disciplines such as entomology, nutrition, microbiology and others, for researchers in multiple countries (Bliss 1935a, b, c, 1939, 1940, 1941; Bliss and Cattell 1941, 1943). This was a very significant tactic as it demonstrated intellectual information transfer planning, communication and coordination. In contrast, the supporters of hormesis were never organized, lacked a plan and never seemed to understand that those advocating the threshold model actually had one.

Fifth—NCI adopts the “constrained” probit in carcinogen assessment, denying hormesis possibility: thus, NCI introduced cancer risk assessment modeling in 1943 with the publication of Bryan and Shimkin (1943). This is significant because the data displayed a J-shaped dose response with a lower tumor incidence at the low doses than controls, yet these findings were ignored in the modeling as the regression line was constrained to be fit through the origin, following the Probit model with the Fisher addendum of several years before.

Sixth—homeopathy’s demise and its linkage to hormesis: the homeopathic movement had also entered into profound decline, especially in the US, during the 1920s and 1930s when most of its medical schools were closed due to the notable and enduring criticisms of the Flexner report. Its decline reinforced the criticisms of Clark on Schulz and his dose response model.

Seventh—hormesis research was not organized: as noted above in number three, hormesis interested researchers were never organized, with a plan to advocate for this dose response. They were non-ideological scientists interested in testing hypotheses related to their field. They were not scientific “soldiers” in the battle between traditional medicine and homeopathy, as Clark and some others seemed to be. Simply put, the hormesis interested researchers were acting as scientists. Further, the fact that essentially most of these earlier researchers drifted into other scientific or administrative challenges left this area of research with no opportunity for guidance, leadership and advocacy and further supports the view that they were non-ideological.

Eighth—hormesis was misunderstood by government and scientific leaders: The biphasic dose response perspective became further damaged when debates occurred over whether this stimulation was a direct response or one due to a compensatory response to prior damage. This led to a near total denial of the low dose stimulatory concept as leaders in the biomedical field concluded wrongly that only compensatory stimulation occurred and that this response was not “real stimulation”, dismissing its potential significance.

Ninth—the long influence of Clark: Clark’s Handbook on Pharmacology with its criticism of homeopathy and Schulz was a striking multi-edition success, being produced in new editions for nearly 30 years after his death. Clark’s power and influence continued to shape the field long after his death.

Tenth—Continuity of threshold model to the next generations: the first generation of toxicologists and regulatory scientists in the US for the most part were pharmacologists who graduated from medical schools. These pharmacologically oriented toxicologists became scientists, trained in the Clark tradition. For example, Arnold Lehman received his MD from Stanford in 1936, became the head of the Pharmacology Division within the FDA in 1946 and helped to establish the Society of Toxicology in 1961, being named its honorary president in 1961–1962. Many other early leading toxicologists were similarly educated. The intellectual and functional “take over” was soon complete as future generations of biomedical scientists would never be exposed to Schulz and his hormesis concept. Within one generation, the hormetic dose response concept was nearly eliminated while the threshold model began a 70 year reign (Calabrese 2007).

Summary

The history of the dose–response provides important lessons to the scientific community. It was shown that powerful interests (e.g., the traditional medicine of the 1920s–1940s) and highly prestigious scientists (e.g., Alfred J. Clark) using the prodigious talents of certain scientists and statisticians (e.g., Fisher, Bliss and Gaddum) established and “institutionalized” a dose response model that would guide the biological and biomedical sciences and clinical practices to the present. Clark also found a way to intellectually diminish the leading opposition, taking advantage of the fact that homeopathy was already in a weakened state and that Schulz was well into retirement, making this takeover effort all the easier. Clark and his talented colleagues then refined the newly created Probit to serve two needs: adding credibility to the threshold model while excluding the hormetic interpretation from the process. This key paper (now with nearly 800 citations) was a crucial factor affecting how studies would be designed, data analyzed and models and risks estimated for decades to come.

A key and perhaps overriding feature in promoting the threshold model, at the expense of the hormesis model, was the significance of an appeal to authority, especially in that era in which the scientific community was probably about 5–10% of the present size.

While it is likely that most, if not all, of Clark’s colleagues may have shared his views on homeopathy, it was

he who most visibility expressed it, a fact noted by the Nobelist Dale in his commentary following Clark's untimely death (Clark 1985). Thus, his strong views were known and his authority was considerable while being further enhanced by the collaborative efforts of the legendary RA Fisher. Given the disorganization of the possible opposition and the high status of the threshold group, success would be fast and essentially complete, and so it was.

The fact that generations of scientists and government regulators assumed that the threshold dose response model was valid led them to impose this “untested assumption” on their experimental studies and on societal health standards. The model also became that which was exclusively taught to generations of students. In addition, many attitudes and beliefs about the opposition model, that is, hormesis, followed from the false information and tactics of Clark by linking this model to the high dilutionist wing of homeopathy, further marginalizing its status in all respects (e.g., inclusion in textbooks, teaching, grants, research, professional positions, regulations, and clinical practice).

Today, the data indicate that the threshold dose response model has been shown to have serious and general limitations. Its failure to predict accurately in the low dose zone is now well documented. If the threshold model can not reliably predict low dose responses what is its continuing utility to clinical medicine and environmental regulation, let alone what has been the damage that following this failed model has already caused. The data therefore indicate that it is no longer justifiable to base drug safety evaluation and chemical hazard and risk assessment on the threshold dose response model as well as linear at low dose models that can not be validated. Moreover, the spate of hormesis papers over the past decade indicates that it can account for many responses in the low dose zone within a detailed mechanistic context. The time has come for a broad scale re-evaluation of the nature of the dose response in the low dose zone. It is time to chart a new course that is tested, vetted and closer to the truth.

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