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Radiation hormesis: the demise of a legitimate hypothesis

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This paper examines the underlying factors that contributed to the marginalization of radiation hormesis in the early and middle decades of the 20th century. The most critical factor affecting the demise of radiation hormesis was a lack of agreement over how to define the concept of hormesis and quantitatively describe its dose-response features. If radiation hormesis had been defined as a modest overcompensation to a disruption in homeostasis as would have been consistent with the prevailing notion in the area of chemical hormesis, this would have provided the theoretical and practical means to blunt subsequent legitimate criticism of this hypothesis. A second critical factor undermining the radiation hormesis hypothesis was the generally total lack of recognition by radiation scientists of the concept of chemical hormesis which was markedly more advanced, substantiated and generalized than in the radiation domain. The third factor was that major scientific criticism of low dose stimulatory responses was galvanized at the time that the National Research Council (NRC) was organizing a national research agenda on radiation and the hormetic hypothesis was generally excluded from the future planned research opportunities. Furthermore, the criticisms of the leading scientists of the 1930s which undermined the concept of radiation hormesis were limited in scope and highly flawed and then perpetuated over the decades by other 'prestigious' experts who appeared to simply accept the earlier reports. This setting was then linked to a growing fear of radiation as a cause of birth defects, mutation and cancer, factors all reinforced by later concerns over the atomic bomb. Strongly supportive findings on hormetic effects in the 1940s by Soviet scientists were either generally not available to US scientists or disregarded as part of the Cold War mindset without adequate analysis. Finally, a massive, but poorly designed, US Department of Agriculture experiment in the late 1940s to assess the capacity for low dose plant stimulation by radionuclides failed to support the hormetic hypothesis thereby markedly lessening enthusiasm for research and funding in this area. Thus, the combination of a failed understanding of the hormetic hypothesis and its linkage with a strong chemical hormesis database, flawed analyses by prestigious scientists at the critical stage of scientific research development, reinforced by a Cold War mentality led to marginalization of an hypothesis (i.e., radiation hormesis) that had substantial scientific foundations and generalizability.
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Introduction

There is little question that the radiation hormesis hypothesis had considerable support in the peer-reviewed, experimental and clinical literature during the first 50 years after the discoveries of X-rays and radionuclides. As was presented in the previous paper,[1] this support was well founded based on the quality of the studies, reproducibility, generalizability of the findings, and the remarkable similarity of the hormetic dose-response relationship between chemical and radiation effects. However, there is also little question that the radiation hormesis hypothesis not only never achieved the status of a central core dose-response hypothesis within the field of radiobiology and health, but was relegated to a very tenuous hypothesis status that was never taken very seriously as is evidenced by its omission from all leading radiation health and toxicological texts, its lack of inclusion within symposia at leading scientific society conferences and lack of consideration by regulatory agencies. This paper set forth to examine why the concept of radiation hormesis which had a strong and generalizable scientific foundation up the 1940s became a marginalized hypothesis within the US and western countries.

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Factors affecting the demise of radiation hormesis

The underlying factors for the demise of radiation hormesis are, as expected, complex, multiple factorial, and dynamic entities that differentially affected the hormetic hypothesis over the first half of the 20th century. Despite this complex web of interacting factors affecting the acceptance of hormesis as a legitimate scientific hypothesis, it is both important and possible to prioritize the influential factors affecting the rejection of this hypothesis and to clarify to some degree the interaction of these factors. While it is tempting to look outside of the limitations of the radiation hormesis hypothesis to a grander conspiracy theory undermining radiation hormesis, it is best to consider the hypothesis itself and how its limitations may have contributed to its own demise before considering external, although potentially important, factors.

Experimental design challenges

The overwhelming data on hormetic responses in well-designed studies indicate that the maximum stimulatory response is quite modest, being only about 30–60% greater than the unexposed control.[2,3] In addition, the maximum stimulatory response is relatively close to the toxic threshold [e.g., the no observed adverse effect level (NOAEL), zero equivalent point (ZEP)], that is, a factor of only 4–5-fold (Figure 1). This quantitative relationship, even if assumed to be real, placed great constraints on the hypothesis because it created the need for more powerful study designs, especially for an adequate number of properly spaced doses below the NOAEL; furthermore, concern over distinguishing normal variability from an apparent modest stimulatory response affected factors such as endpoint selection, sample size, and statistical power.

These experimental dimensions of hormesis made it more difficult to establish evidence to support this hypothesis and increased the level of effort by requiring more treatment groups per experiment and more subjects per treatment group. Given those constraints, it was certainly easier to conduct experiments at higher doses and define the upper end aspects of the dose-response curve. Such high dose experimentation was less controversial, more reproducible, required less resources, and was more certain of being published. This set the stage for failure for the hormetic hypothesis since hormetically oriented research offered more professional risk along with few obvious benefits and limited economic applications. Thus, the burden of proof fell on an unorganized (e.g., no scientific society) and a limited number of scientists to establish the data that were to evaluate radiation hormesis as a biological hypothesis. Radiation hormesis was to become an easy target for legitimate methodological critiques that demanded objective answers that were based on proper study design and statistical power.

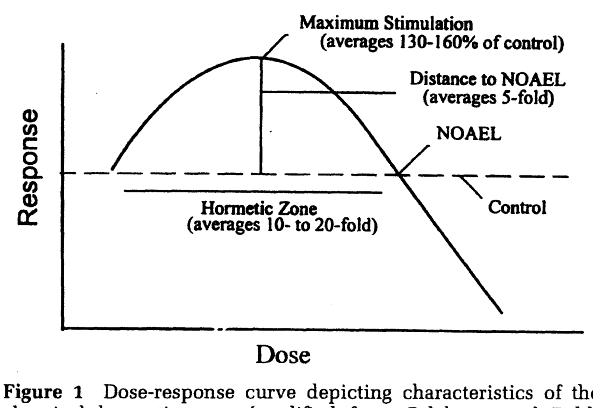

Figure 1 Dose-response curve depicting characteristics of the chemical hormetic zone (modified from Calabrese and Baldwin[3]). Abbreviations: NOAEL=no observed adverse effect level; LOAEL=lowest observed adverse effect level; ZEP=zero equivalent point

Lack of awareness of research on chemical hormesis

In addition to its inherent limitations as a dose-response theory, the opportunity to provide support for this perspective by citing the substantial and earlier supportive work on chemical hormesis was essentially totally ignored by those publishing in the area of radiation hormesis. This lack of linkage between radiation and chemical hormesis denied those radiation scientists interested in the hormesis concept the opportunity to become aware that similar low dose stimulatory phenomena had been observed by numerous highly regarded scientists, over nearly three decades of previous research. If such information had been considered by the critics of radiation hormesis it is likely that their perspectives could have been altered.

By 1910, the concept of chemical hormesis was well established in the areas of plant and algal biology, fungal responses, and bacterial growth.[1] In fact, the basic hormetic curve (i.e., β-curve) was clearly published as early as 1905 by True and Oglevee in the journal Botanical Gazette.[4] By 1920, low dose stimulation had been extended to insect responses to toxic substances and by the 1930s hormetic responses by bacteria to low doses of toxic substances were highlighted in leading microbiological texts along with adequate documentation.[5] In fact, the concept that this low dose stimulation represented an overcompensation to a disruption in homeostasis was first proposed by Townsend[6] in 1897 and then supported by Branham[7] and Colley.[8] This was also an important methodological concept since it required a proper temporal component to such experiments thereby adding further resource and time demands on study protocols.

Despite the substantial supportive information on low dose stimulatory responses to highly diverse chemical agents, none of these papers were ever cited in the research that comprises the database on the historical foundations of radiation hormesis.[9] The only direct linkage between the chemical and radiation hormesis areas is believed to be that of FL Stevens who published evidence of low dose chemical stimulation of fungal growth in 1898[10] and then 30 years later a series of highly influential papers on low dose UV radiation as a stimulatory influence on fungi.[11–15] However, the later work of Stevens, having moved from the University of Chicago to the University of Illinois, never cited his earlier stimulatory work on chemical agents.

Scientific criticisms of radiation hormesis

One can observe the type of framework being established by the 1920s and 1930s in which criticisms of low dose stimulatory responses emphasized poor study design features, inadequate sample size, and inconsistent reproducibility.[16,17] This view became the dominant technical perspective in the mid-1930s following deafening criticism on radiation hormesis' strongest area (i.e., X-ray induced plant growth stimulation) by Edna Johnson, Professor at the University of Colorado in her capacity of invited author in the highly prestigious volume of the NRC on the toxicological effects of radiation.[17] In many ways, such criticism was reinforced by Professor Elizabeth Smith from the University of Wisconsin writing in the same prestigious publication who critically assessed the effects of radiation on fungal growth.[18] However, in the case of Smith,[18] she recognized that stimulation of mycelium growth was a verifiable phenomenon except that it only occurred AFTER the UV-induced initial damage with stimulation representing an overcompensation response.

Defining the concept of hormesis

Such a recognition of the stimulation not being a direct one, but only in response to damage, was viewed by some as a direct refutation of the hormesis hypothesis. For example, while Manfried Fraenkel argued that small doses can stimulate by a direct biopositive action of the X-rays,[19] Holzknecht and Pordes denied the possibility of a direct stimulatory response without simultaneous damage.[19] This confusion over whether the stimulatory response of the Arndt-Schulz Law was a direct one or only in response to damage became an important issue that was still highly visible several decades later.[19,20] Given the predominant role of Holzknecht in the early development of the field of medical applications of X-rays (i.e., he studied with Roentgen for 3 years; he established the first method of measuring X-rays; he created the International Society of University Professors of Medical Radiology; he was the first European professor of medical roentgenology),[21] such disputes remained active and further confounded the issue of hormesis since it was not clear, even to the established experts and advocates, exactly what constituted an hormesis stimulation (i.e., direct or indirect).

The lack of understanding of hormesis continued to be a critical factor in its rejection as the field of radiation health rapidly matured into the 1940s. For example, the prestigious Harvard professor and first Director of the Division of Biology and Medicine at the US Atomic Energy Commission,[22] Shields Warren, continued to promote the concept of Holzknecht and Pordes by stating that 'the assumption that small doses of X-ray or radium radiation are stimulatory (the Arndt-Schulz 'law') is invalid. The slight evidences of proliferative activity offered as evidence by the proponents of this hypothesis are in fact only reparative responses to the injury that has been done'![23] Recognition of reparative overcompensation due to radiation-induced damage was proposed in 1920 by Hektoen,[24] head of Pathology at the University of Chicago, with respect to antibody production, and by Pohle,[25] Koga,[26] Teneff and Stoppani,[27] and Schurer[28] for enhancement of reticuloendothelial activity. The key element in this assessment is the incorporation of an adequate temporal component in the study design. For example, in the case of Schurer[28] phagocytosis was inhibited during the initial 4 h after exposure to X-rays; however, by 8 h after treatment this condition had yielded to one of enhanced phagocytic activity. These findings indicating an overcompensation response to an initial toxic insult have been supported in later reports of Bloom and Jacobson,[29] Dunlop,[30] and Taliaferro and Taliaferro.[31] These radiation-induced reparative responses were also comparable to the responses reported by Smith[20] for UV-induced fungal mycelium growth. That is, that enhanced growth was observed only after damage and that it was necessary to include a repeat measures design to properly describe this phenomenon.

Thus the rejection of the Arndt-Schulz Law by prominent individuals such as Warren over the observation that the stimulatory response was merely a response to damage rather than a direct stimulatory effect was perhaps the critical judgmental factor in marginalizing the hormesis concept. In fact, these dismissing individuals neglected to hypothesize that the process that they were marginalizing was a basic feature of the toxicologic dose-response curve observed in plant and animal models without regard to whether the damage was induced by chemicals or radiation. The fact that the 'stimulation' (i.e., overcompensation) was modest, consistently distanced (i.e., 3–5-fold) from the traditional NOAEL, and with a modest overall range of about one order of magnitude supported the fact that this response was likely due to a limited induction of damage. Rather than offering a refinement of an hypothesis (i.e., the Arndt-Schulz Law) to incorporate an appropriate temporal experimental feature in the study design and to recognize the possible or likely role of an overcompensation reparative response to account for the quantitative aspects of the low dose stimulatory response, the rather astonishing collective conclusion was to reject the Arndt-Schulz Law and the hormesis concept on the simple equivalent of a yes or no vote.

It is ironic that over 50 years later that definition of hormesis that is most prominently articulated is that of an overcompensation response following a disruption in homeostasis.[32] This is the very concept that was recognized as being most consistent with the available data in the 1930s and 1940s and yet dismissed because it was not a 'direct' stimulation. It thus appears that Warren and others have derived that proper scientific concept, but they marginalized its role to the point of irrelevancy, as is seen in the following paragraph on how the concept became ignored in the conceptual development of the dose-response relationship.

Of particular importance to the field of radiation hormesis was the fact that the concept of dose-response, as developed by leading biostatisticians, occurred in the mid-1930s through the 1940s. These authors totally ignored the concept of hormetic dose-response relationships and developed mathematical models more catered to fit high dose data sets. Of further note is that the well-known biostatistician Bliss who developed biostatistical models of radiation effects data worked closely with the world-renowned pharmacologist AJ Clark, an ardent and articulate opponent of the Arndt-Schulz Law, especially influential in European circles (see Clark[33]). The collaboration of the laboratory-bench scientists with the biostatistician as partners[34,35] in the articulation of the nature of the dose-response relationship was a powerful and dominating combination that would long suppress challenges to the so-called dominating toxicologic paradigm of linear or threshold dose-response relationships.

Hormesis and economic implications and charlatans

While much confusion ruled the debate over whether hormesis or low dose stimulation following radiation exposure occurs, the fledgling field of radiation hormesis was further hampered by both legitimate and charlatan-like desires to exploit the concept of low dose stimulation for a range of applications including the enhancement of agricultural production[36–38] to providing a rejuvenating quality to human life.[39] For the most part, these attempts at commercialization of the hormesis concept never really were sufficiently convincing to establish a long-term successful commercial presence. Furthermore, the concept of low dose consumption of radioactivity became embodied in what was called 'mild radiation therapy' to separate it from the more destructive treatment in the case of tumor destruction therapies.

According to Macklis,[39] the mild radiation therapy approach had its foundation in the American homeopathic and physical medicine movements of the late 19th century. Mild radiation therapy was more associated with endocrinology than oncology and was based on the premise that low doses of radiation could serve as a powerful metabolic catalyst.[39,40] The principal belief of the mild radiation therapists was that the beneficial effects were mediated by the alpha particles of the radium nucleus. This was linked with the use of hot springs throughout Germany, Italy, and France which had been touted to cure numerous illnesses. Once radon was found in 1903 in the Gastein Springs by the famous German chemist Justus von Liebig, alpha particle emitting isotopes became a great rage, becoming used as natural elixirs which were believed to provide direct energy transfusions to depleted organs.[39]

As Macklis[39] noted, the discovery of the therapeutic uses of radon marked the start of an important era of radioactive patent medicines. Since consumption of mineral water from hot springs having high background radon levels had a long history without known adverse health effects, it was then assumed that consumption of long-term use of small quantities of radon would also likely be without harm in commercial products. Supportive of this assumption was the study of the German physiologist, George Wendt, who claimed in 1929 that moribund vitamin-depressed rats could be rejuvenated following radium exposure. In fact, the radium was prescribed for nearly three decades with numerous commercial products on the market claiming to treat just about every human ailment imaginable. However, according to Macklis,[39] the reign of the radioactive elixirs and alpha particle emitting liniments came to an abrupt halt on March 31, 1932 when the well-known millionaire industrialist Eben M Byers died a highly disfiguring death from radium induced bone cancer which received first page coverage in the New York Times, 'Eben M.

Byers Dies of Radium Poisoning!' Byers had consumed the radium containing product Radithor on a routine basis for several years.

Such publicity of the death of the well-known Byers and the somewhat earlier recognition of osteosarcoma in female radium dial painters marked a turning point leading to the demise of mild radium therapy. The mounting criticism of scientists such as Johnson[17] and the negative publicity such as the Byers tragedy and the lack of successful commercial applications went a long way to undermine the scientific and medical belief in the stimulatory effects of low level radiation effects.

At the same time, the use of low levels of X-rays had been employed to treat many human diseases with an apparent record of good success (see reviews by Desjardins[41–45]). This application of X-ray treatment was usually a single low dose treatment that was quite distinct from that used at higher doses for tumor destruction therapies. Typically, a single dose of 50–100 r was all that was used to successfully treat a large variety of human diseases such as furuncles (boils), carbuncles, pneumonia, sinusitis, gas-gangrene, and others. However, the use of even successful low dose X-ray therapy was severely challenged during the early decades of the 20th century by attractive alternative new therapies such as vaccines, antiseptics, and antibiotics. This was especially true from the 1930s onward as sulfa drugs, penicillin, and streptomycin and their derivatives became more available.

Opposing scientific leadership

The availability of new magic chemical bullet treatments, the concern over toxicity at high doses, and the knowledge as of 1927 by Muller that X-rays could cause mutations, all contributed to a very precautionary era of radiation use and exposure. These developments occurred very closely in time and with reinforcement of the limitations of the low dose stimulation theory of radiation. In addition, there appears to have been no powerful intellectual counterforce to defend the radiation hormesis perspective and at sometime in this temporal window of crisis (1930s–1940s), radiation hormesis became rejected by science, medicine, and society and therefore became marginalized. It is interesting to note that the most likely individual to step forward and become a visible advocate for radiation hormesis was Benjamin M Duggar, a professor at the University of Wisconsin. Professor Duggar had studied under the internationally renowned German botanist Pfeifer in the late 1890s at the University of Lipzig and became interested in various types of adaptive responses and low dose stimulatory effects. Upon his return to the US in 1896 he proceeded to finish his PhD at Cornell University and published a very significant paper on low dose chemical stimulation on fungi.[46] Duggar eventually moved to Wisconsin and became the mentor of the well known Alexander Hollender, co-founder of the Environmental Mutagen Society (EMS), and the source of acknowledged guidance for University of Wisconsin Professor Elizabeth Smith in her research in UV stimulation of fungal growth. Duggar also was the editor of the NRC publication[47] in 1936 when Johnson[47] and Smith[18] authored their highly influential articles. Duggar was to later move on to American Cyanimide, assisting in the search for new antibiotics after the remarkable work of Dubos and Waksman.[48]

Nonetheless, Duggar had a long career of leadership in the area of low dose stimulation, had achieved an influential position, had the respect of leading experts and the NRC, and yet he did not accept the challenge at the critical juncture to advocate hormesis. In addition, it should be noted that the criticisms of Johnson[17] could have been addressed in a very direct manner by Shull, who along with Mitchell,[49] published a widely cited study on the low dose stimulatory effects of X-rays on multiple plant species. As noted by Calabrese and Baldwin,[9] Professor Shull helped guide Edna Johnson's dissertation in the mid-1920s when she was a student at the University of Chicago. His latter widely-cited work[49] directly contradicted the conclusions of Johnson and others who emphasized high dose radiation experiments while he established that the nature of the biological response was principally a function of dose with high doses of X-rays causing inhibition and low doses stimulation. However, neither Johnson or Shull ever directly confronted each other on this issue in print, and even more oddly, essentially only tangentially cited each other's work.

Other factors

After the 1930s the field of low dose stimulatory research became subsumed within the unfoldings of World War II and the development and concerns of the atomic bomb. The course of research was also affected by the development of new gamma products from fission reactions making radium studies in low dose studies almost passé with cesium becoming prominent.

At the same time the issue of low dose stimulation became a progressively more central theme among eastern block biomedical and agricultural researchers, especially among a large number of Soviet scientists. In the 1930s–1950s Soviet scientists published a remarkable series of papers on low dose stimulatory responses to X-rays and later X-rays and gamma rays. This research was viewed with suspicion by many US and western scientists because of both political influence on many aspects of Soviet science as well as frequent inadequacies in the reporting of research methods by Soviet scientists. However, most US scientists had little access to and knowledge of these findings since their papers were usually published in the Russian language in Soviet journals having poor circulation in the west. In fact, one of the more significant works of the Soviet scientists of 1946 addressing low dose stimulation was not translated into English until 1960,[50] reflecting the time lag between east-west scientists, even in areas of considerable importance.

Further undermining of scientific support of the low dose radiation stimulatory hypothesis were the results of the then famous US Department of Agriculture (USDA) 22 center, three radionuclide study in 1948 to assess the stimulatory hypothesis in 20 plant species.[51] The data, which were generally not supportive of the stimulatory hypothesis, are believed to have had a major impact on how the concept of hormesis was to be considered not only by the scientific community but also by potential US and international funding agencies in the west. It was unfortunate that this remarkably large study undercut the hormetic hypothesis since it only utilized from one to three doses per experiment without providing any information on how doses were selected for any of the species studied. Thus, this was an example of a disproportionate influence that had major long-term impact since it was such a massive study, conducted under the leadership of the US government at a time of major political uneasiness with respect to radionuclides and their usefulness.

The relegation of hormesis to a marginalized status was significant because it achieved this position just at the same time that the US government was organizing a national radiation research program under the influence of the NRC. Thus, leading researchers were not encouraged to pursue the hormesis tract nor would low dose stimulatory hypotheses be granted any reasonable priority. The continuation and reinforcement of such practices were clearly seen with the program activities of the Radiation Research Society throughout the 1950s and 1960s in which this topic never surfaced at national meetings.[22] This organization was key in bringing together the major leaders of the radiation health research community, including the likes of Alexander Hollander, Gino Failla, and others, and especially guided US research in this critical area. Within this highly influential group there was no leading advocate for radiation hormesis.

It should be noted that the world-renowned radiation physicist Gioacchino (Gino) Failla published a paper in 1922 which reported that low doses of radium enhanced the growth of mice.[52] These authors offered the following comments about the effect of radiation dose on the growth of mice: '(a) Sufficiently small doses of radiation accelerate the growth of suckling white mice. (b) A larger dose of the proper value will have no influence on the body growth of mice. (c) A still larger dose, up to a certain limit, will retard growth, but the animals will eventually attain normal size. (d) Still larger doses cause premature death. Similar results have been obtained before in experiments on seeds and plants, also on lower forms of animal life exposed to X-rays. From these it is commonly assumed that the action of radiation on the living cell follows the same general law which governs the action of all anesthetics, as well as chemical, mechanical, and electrical stimulants; that is, if some form of energy is gradually brought to bear on the cells, at first they may be stimulated to greater activity, then their normal function may be arrested, and finally they may be destroyed.'

One might have thought that with such support for the hormetic perspective Failla could have been the scientific leader that radiation hormesis needed at this critical junction. Failla, who obtained his doctoral degree at the Sorbonne in 1923 under Madame Curie, became one of the most noted leaders in the field of radiation and health physics in the US. He was the recipient of numerous prestigious achievement and career awards and the co-founder and second president (1953–1954) of the Radiation Reseach Society (see Failla obituary by Marinelli[53]). Following his death, the Society created the annual Failla Lecture which is published in his honor.

The question is why did Failla not become a leading supporter of radiation hormesis since he was a strong and effective leader of so many other important aspects of the field? First, the above cited and highly supportive paper on hormesis[52] was published in 1922, one year prior to Failla's completing his dissertation. Consequently, he had relatively young professional status at that time. Second, he was principally a radiation physicist and devoted his activities to that area. Later he did co-publish a paper with Henshaw in 1931 on the effects of X-rays and gamma rays on wheat.[54] This extremely well designed and conducted study was conducted using high doses of radiation and induced inhibitory growth. Most of his other research was directed to physical phenomena and not only low dose response experimentation. Much of his public service activities were devoted to worker protection and establishing safe exposure standards. Thus, even though Professor Failla had a knowledge of the concept of hormesis, published supportive original data on this topic, and was aware of other supportive findings in the literature, he pursued other interests more germane to his training in radiation physics leaving hormesis research behind. While it is unclear how he considered the hormesis hypothesis in his later years, his early positive encounter with it never materialized into Failla being either an advocate or critic of hormesis.

Arnold H Sparrow of Brookhaven National Laboratories and later president of the Radiation Research Society reported on the capacity of gamma radiation to stimulate plant growth.[55,56] In fact, Sparrow was influential in securing the translation of the above mentioned 1946 Russian study into English in 1960. Also, the highly regarded Professor Karl Sax of Harvard University published two limited but important and supportive literature reviews on the stimulatory effects of X-rays and gamma rays on plants in 1955 and 1963, respectively.[57,58] In fact, it is noteworthy that Sax's graduate student Sheldon Wolf in the mid-1980s was a co-discoverer of the concept of adaptive response with radiation. However, the involvement of Sax with the issue of hormesis was limited to the modest reviews and was not of a transforming nature to the field.

Discussion

Why did the radiation hormesis hypothesis become marginalized in the scientific community in the first half of the 20th century? While the reasons were numerous, it definitely could and should have been avoided. As the previous assessment of Calabrese and Baldwin[9] has shown, the data were available to have secured a firm place for the radiation hormesis as a legitimate hypothesis. Yet a combination of factors acting collectively led to its undermining (Table 1). It appears that much of the 'blame' can be placed primarily on the lack of critical reviews of the available literature on low dose stimulation by chemical agents and radiation by the scientific community, little apparent communication between those researching the biological effects of chemicals and radiation at low levels, a heavy reliance on the judgment of a few scientists of solid reputation (e.g., Johnson, Warren) to analyze the main body of radiation hormesis evidence, and lack of scientific leadership to step forward to challenge 'authoritatively' erroneous and perpetuated conclusions[59,60] by other recognized experts. Furthermore, the criticism of radiation hormesis by leaders such as Johnson[17] and Warren[23] which addressed agricultural and medical perspectives, respectively, occurred precisely during the time period US federal agencies were enhancing research on the biological effects of radiation. Such timing of events relegated the hormesis hypothesis to a position out of the mainstream of power and influence.

These central factors were reinforced by the progressive recognition within the scientific community, governmental agencies, the general public and the media of the adverse effects of high and perhaps much lower doses of radiation and the failure of exaggerated commercial and health claims of low dose exposures.

It is hoped and expected that a scientific hypothesis will rise or fall on its own merits. We have found that the outcome of this process for radiation hormesis was complicated by lack of available knowledge, as well as scientific, medical, societal, and political factors operating within a dynamic temporal context. While the concept of hormesis is now being revived as a biological hypothesis, the thought that an hypothesis with

Table 1 Summary of the factors involved in the demise of the radiation hormesis hypothesis

Factors
1. Hormetic responses are modest and can be hard to reproduce without an adequate study design
2. Researchers in the radiation area did not link hormetic findings to the more substantial and earlier chemical hormesis database
3. Confusion existed over what hormesis was even among supporters
4. Prestigious scientists offered flawed criticism that was perpetuated throughout the literature, and negatively influenced funding programs
5. Low dose stimulation failed to be a commercial success in various areas such as agriculture reinforcing the above criticism
6. Biostatistical modeling ignored hormetic responses linking only with the alternative traditional dose-response paradigm
7. No leading/respected scientist supportive of hormesis countered opposition
8. Radiation research funding emphasized high dose effects, ignored low dose effects
9. Supportive evidence in foreign literature was not generally available to US scientists
10. As a result of WWI and WWII US science became dominant; there was a strong bias to exclude hormesis
11. Soviet support of hormesis was largely disregarded in the Cold War
12. Major US test of hormesis in plants by USDA in 1948 failed to support hormetic claims; this poorly designed study had a long-term dominant influence on governmental programs

substantial supportive data could be so quickly marginalized without either notable scientific refutation nor with at least a modest but visible debate within the scientific community is a sobering thought.

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