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Historical foundations of hormesis

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The present paper provides an historical assessment of the concept of hormesis and its relationship to homeopathy and modern medicine. It is argued that the dose–response concept was profoundly influenced by the conflict between homeopathy and traditional medicine and that decisions on which dose–response model to adopt were not based on "science" but rater on historical antipathies. While the historical dispute between homeopathy and traditional medicine has long since subsided, their impact upon the field has been enduring and generally unappreciated, profoundly adversely affecting current drug development, therapeutic strategies and environmental risk assessment strategies and policies. *Homeopathy* (2015) ■, 1–7.

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Introduction

The history of hormesis is a long and entangled one, but with a vibrancy that extends from the 1880s to the present. It is also a history that needs to be understood since it affects scientific, biomedical, therapeutic and regulatory activities today, all disciplines that utilize and apply dose response concepts. This is particularly the case since hormesis has long been ignored and/or not appreciated by the fields of pharmacology, toxicology and clinical medicine[1,2] having generally failed to be included in historical assessments of the leading textbooks, even those that devote specific chapters to such histories (e.g. Casarett and Doull's Toxicology). Yet, it is in the discovery, debate and rejection of the hormesis concept by the medical community in the later decades of the 19th and early decades of the 20th century that lead to the development and applications of the threshold and linear dose response models and their dominance in toxicology, pharmacology and clinical medicine throughout the 20th century to the present.[3–5] It is the contention of this paper that the scientific and medical communities made a profound mistake on the nature of the dose response, rejecting the even the possibility of hormetic-biphasic dose responses, due not to scientific considerations, but to longstanding historical antipathies between homeopathy and what today is called traditional/mainstream medicine. That is, in their victory and dominance over homeopathy during the first half of the 20th century the scientific and medical communities got the dose response half right, correctly characterizing responses at high doses while getting the critical (and more difficult to discern) low dose response wrong. The present paper will explore the history of the dose response, how and why the scientific and medical communities rejected the hormesis concept, getting the dose response wrong, what this historical error means for treating patients, the public health and environmental risk assessment and how this error can be corrected. While it may be difficult to conceive of the possibility that the scientific and medical communities made a critical mistake on a fundamental pillar of their discipline, this paper will show how and why this occurred and why this fundamental error continues to be sustained to the detriment of society, especially by regulatory agencies.

The dose response concept: origins and controversies

The early history of the dose response is closely associated with the life and times of Hugo Schulz, a professor of pharmacology and toxicology at the University of Greifswald in northern Germany from 1882, at the age of 29, and for the next 50 years. Prior to his arrival at Greifswald, Schulz did post-doctoral research at the University of Bonn, under the direction of Carl Binz (1832–1913), a pharmacologist well known for characterizing the toxicological and pharmacological effects of quinine.[6] While Schulz was studying at Bonn, there was much concern over the use of antiseptics as a means to enhance the success of surgical outcomes. Since 1865 John Lister had recommended the use of carbolic acid to reduce the risk of infections following surgery but this agent was associated

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with various types of toxicities, even deaths in unusual instances.[7] Thus, Binz directed Schulz to assess the potential of eucalyptus oil as an alternative to the use of carbolic acid following surgery as well as for the treatment of nonsurgical wounds. However, after extensive human testing it too was unacceptable due to its highly irritating nature, a finding consistent with those of Lister.

Upon moving to Greifswald, Schulz expanded his search for an effective antiseptic, initially via use of an experimental microbiological model, assessing the metabolism of yeast. Schulz was expecting that the highly toxic disinfectant agents that he was going to evaluate would induce toxicity at all the doses tested, showing a progressive dose dependent toxicity. Schulz's study design was extremely robust as it included not only a substantial number of doses but also series of time interval evaluations. While all the agents tested displayed toxicity at high doses, they displayed an enhancement of metabolism at the lower doses. This surprised Schulz and made him think that he had done something incorrectly during the experimentation. Thus, he set forth to replicate the experiments many times so that he could resolve whether the unexpected findings were spurious or whether they were reliably reproducible. After considerable follow up evaluation in which the low dose stimulation was consistently observed Schulz was convinced that the original findings were able to be reproduced even though quite unexpected and inexplicable.[7] This was a significant finding having the potential to link his work to the efforts of Lister, who was now internationally famous.

At approximately the same time as his disinfection research, Schulz was following up on the findings of a rather striking paper in the homeopathic literature which had shown that the therapeutic use of the plant extract called veratrine was successful in the treatment of gastroenteritis.[8] Since Robert Koch's laboratory had just identified the bacterial causative agent Schulz obtained the culture and attempted to determine if the veratrine affected the cure via the killing of the causative organism. To his surprise Schulz was not able to kill the disease causing bacterium or inhibit its growth regardless of the dose employed.[6] Schulz wondered then how the veratrine was able to affect reported cures.

While his first two research initiatives yielded unexpected findings they did not seem to be related, that is, until he had a significant discussion with his colleague Rudolph Arndt in 1885. During their meeting, the two men came to the conclusion that the veratine-induced therapeutic response was not due to its killing the bacteria but via its capacity to induce an adaptive response at low doses that lead to the elimination of the infection. They then drew upon the findings of the disinfectants on the yeast, seeing the biphasic dose response as a manifestation of same general type of adaptive response. Thus, they concluded that most agents, including homeopathic drugs, display a biphasic dose response, characterized by a low dose stimulation and a high dose inhibition. Schulz concluded that he had discovered the explanatory principle of homeopathy. He soon shared this interpretation with the local homeopathic and medical communities, becoming hero to the former and a traitor to the latter.[6,9] Whether he was aware of the implications of his decision, he soon found himself marginalized and ridiculed by members of the medical establishment, including his medical school colleagues. However, the young Schulz would not relent. He believed that he was correct and would face the professional consequences of which there would be many. Now a 32 year old professor on the cusp of significant academic progression Schulz soon learned that essentially all avenues for professional advancement had ended.[10]

While one might think that Schulz had acted with a high degree of personal courage, and perhaps he did, the implications of his striking pronouncement concerning his discovery of the underlying mechanism of homeopathic therapies, not only profoundly affected his career possibilities but it likewise would have the same deadening effect on the biphasic dose response model that he had discovered in the laboratory[11,12] and now broadly generalized. In fact, the linkage of the biphasic dose response to homeopathy in this manner as its explanatory principle resulted in its rejection by the medical community, and its widespread ridicule and marginalization for the next one hundred years. This meant that Schulz's concept would not be taught, researched or applied to therapies or in governmental risk assessment programs.[4] This type of exclusion would be applied to drugs, chemicals and radiation. Thus, Schulz would have a profound effect on the concept of hormesis. In fact, the net effect of Schulz on the concept of hormesis would be profoundly negative. He made a strategic mistake of incalculable proportions when he linked it to the core of homeopathy, especially knowing full well the hostilities between homeopathy and what is today called traditional medicine.

Ferdinand Hueppe was quick to point out the problem that Schulz had created for the concept of the biphasic dose response.[13] Hueppe, a member of the laboratory of the famous microbiologist Robert Koch, also reported the occurrence of the biphasic dose response but with bacteria. He acknowledged the novelty and primacy of the Schulz findings while criticizing him for associating this concept with homeopathy. He appealed to the scientific and biomedical communities not to reject the concept of the biphasic dose response just because Schulz had linked it to homeopathy. Hueppe asserted that it was a real phenomenon and important. It is obvious in retrospect that Hueppe's arguments were not persuasive as Schulz's concept failed to thrive. One reason is that Hueppe soon left the field of microbiology and developed a strong focus on public health and the role of exercise[14] leaving Schulz and the biphasic dose response to fend for themselves. However, if Hueppe had linked the biphasic dose response to the activities and fortunes of his mentor, Robert Koch, the history of hormesis may have been quite different. Likewise, a similar scenario could be developed for John Lister who had become an internationally acclaimed surgeon, transforming it with his novel antiseptic methods. Schulz's findings with a large number of potential disinfectants were strongly in line with the need of Lister to use

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