BELLE NEWSLETTER

Biological Effects of Low Level Exposures

A Publication for the Northeast Regional Environmental Public Health Center, University of Massachusetts, School of Public Health, Amherst, MA 01003

Vol. 16 No. 1, April 2010, ISSN 1092-4736

HORMESIS AND HOMEOPATHY

Introduction

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This issue of the BELLE Newsletter addresses how, if at all, the concepts of hormesis and homeopathy may be related. It should be pointed out that in the numerous articles I have published on hormesis I have never claimed that the two are toxicologically related. I have argued that Hugo Schulz, the person given the most credit for discovering the hormesis concept, made a major mistake by thinking that he had discovered the explanatory principle of homeopathy. By linking the hormesis concept (not the name) to the medical practice of homeopathy it was my opinion that this was the equivalent of hormesis receiving a scientific "scarlet letter". This opinion was based largely on the homeopathic principles associated with extremely high dilution practices. These practices, which go back to the thinking of Hahnemann, the founder of homeopathy, are clearly not related to the concept of hormesis.

The major challenge that hormesis has had over the past several decades was to be taken seriously by the scientific community. Over 1,200 articles in the scientific literature have been published on hormesis based on a review of the

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Web of Science data base. Over 80% of these articles have been published since 2000. The concept of hormesis has become incorporated into the leading toxicological textbooks (Klaassen and Watkins, 2003; Hayes, 2008) as well as the object of presentations to the BEIR VII committee of the National Academy of Sciences (Calabrese, 2000), the focus of workshops at annual meetings by leading professional societies like the US Society of Toxicology, and the object of special issues of journals (e.g. Aging Research Reviews, 2008; American Journal of Pharmacology and Toxicology, 2008) and conference proceedings (e.g. Environmental Health Perspectives, Dose Response, Critical Reviews Toxicology, Journal of Applied Toxicology). It has been the object of several books (Luckey 1980, 1991; Mattson and Calabrese, 2010; Sanders, 2010). Of particular importance is that several major studies have indicated that the hormetic dose response far outperforms the long revered threshold and linear at low dose models used by regulatory agencies (Calabrese and Baldwin, 2001, 2003; Calabrese et al 2006, 2008, 2010). The key point is that the concept of hormesis is now established in the scientific domain, growing rapidly in interest and influence, being seen as a basic biological concept.

As editor of the BELLE Newsletter I was not inclined to revisit the issue of homeopathy and hormesis. Hormesis was finally shedding the historical misgiving of Hugo Schulz. Furthermore, since I was convinced that the discoveries of Schulz were not even remotely related to homeopathy, I had decided to write an historical article on hormesis and homeopathy in which I would further decouple any possible historical association of hormesis with homeopathy. In this article, I planned to make the case that Schulz's ground breaking research was misinterpreted by him, leading to the confused historical linking of these two concepts. In the course of this research I came across a research initiative by researchers in The Netherlands, highly expert in the study of heat shock proteins, which was explicitly designed to test certain alleged concepts of homeopathy within a standard experimental based modern molecular framework. The timing of the discovery of their research occurred when I was co-authoring a paper with 57 other scientists on the development of an hormetically-based common terminology of biological stress responses (Calabrese et al., 2007). I saw that the research of Wiegant and Van Wijk was conceptually very similar to the concept of post-conditioning hormesis which was first described in this paper on a common terminology. The findings were extended by this group in a series of progressively detailed papers (Ovelgonne et al., 1995; Vanrijn et al., 1995; Wiegant et al., 1998, 1999). Then for unknown reasons they no longer pursued the question, nor did any other group pick on their interesting findings.

I did complete the initial drafting of my paper but it was now significantly different from the one that I had planned. This draft (see finalized paper published in this issue as Calabrese and Jonas, 2010) now was proposing that some types of homeopathic treatment may in fact be examples of post-conditioning hormesis. It made me initially think that I was becoming part of the problem for hormesis, now a century or more after Schulz created the problem. So I put the manuscript aside for several months, and re-read it and all the cited references again. I still thought what I wrote was accurate. I repeated this process again to the same result. I then decided to seek out a few objective critics who agreed with the analysis but who were concerned that this may hurt the chances of hormesis concept being accepted in the scientific community since homeopathy was considered something like witchcraft. I stressed to these critics that very high dilution homeopathy may well be a totally wrong concept but that there was "low" dilution school within the broader homeopathic community in which concentrations of medical treatments are routinely measured, a group that is actually as dismissive of high dilution homeopathy as we are. That is, homeopathy was not monolethic and to characterize it as such was factually incorrect (Calabrese, 2005, 2008).

After several months I decided to send the manuscript to Dr. Wayne Jonas of the Samueli Institute and former director of the NIH's National Center for Complementary and Alternative Medicine, since he has a detailed and unique understanding of homeopathy and hormesis. Dr. Jonas was strongly supportive of the article but suggested ways it could be improved. At that point I invited him to become a co-author. After the manuscript was completed,

we decided to send it to The Lancet for publication consideration. This submission failed to generate interest and it was returned without having received a peer review. I then suggested to Dr. Jonas that we develop a BELLE Newsletter around the paper which would involve inviting a number of experts on the topic to write expert commentaries about the article.

I now invite you to read the manuscript that Dr. Jonas and I co-authored and the expert commentaries, along with our response to the commentaries

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HOMEOPATHY: CLARIFYING ITS RELATIONSHIP TO HORMESIS

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SUMMARY

This paper presents the case that certain types of homeopathic medicine may represent a form of hormesis, that is, either pre or post-conditioning hormesis. An example of a post-conditioning model by van Wijk and colleagues demonstrated successful enhancement of adaptive responses using below toxic threshold doses (i.e. hormetic doses) of inducing agents when administered subsequent to a highly toxic chemical exposure, thus satisfying a basic experimental biomedical standard. Of note is that this model uses exposures within a measurable predicted hormetic range, unlike many forms of homeopathy. This experimental framework (along with a pre-conditioning model developed by Bellavite) provides a possible vehicle by which certain aspect(s)of homeopathy may be integrated into mainstream biomedical assessment and clinical practice.

Key Words: homeopathy, hormesis, dose-response, overcompensation, tissue repair, stress response

INTRODUCTION

Hormesis is a dose-response phenomenon characterized by a low dose stimulation and a high dose inhibition. More accurately, it is a dose-time-response relationship in which there is an initial dose dependent toxicity response followed by a compensatory/rebound response, such that at low doses the response becomes greater than the original background state or control group value[1] (Figure 1). High dose treatment groups that experience much greater damage often do not fully compensate or repair all damage up to the conclusion of the experiment. This dose-time response is what Schulz[2] reported in 1888 in an assessment of the effects of various chemical disinfectants on yeast metabolism. These dose-time effect findings were carefully replicated and extended on the yeast model by Branham.[3] It was recognized that the low dose stimulation was an expression of damage-related, compensatory responses as early as 1897 by Townsend[4] and subsequently by many others regardless of the biological model, the endpoint and agent studied. The kinetics of this process was clarified in detail by Stebbing[5] and more recently reviewed by Calabrese.[6]

Schulz[2] interpreted his findings with yeast responses to chemical disinfectants as providing the scientific explanatory principle of homeopathy, adding further to the considerable controversy in the long-standing and heated turmoil between orthodox medicine (i.e., allopathy) and homeopathy. While the present article will show that the findings of Schulz[2] along with its replication by Branham[3] provide little, if any, scientific support for the medical practice of homeopathy, it will be demonstrated that certain forms of homeopathic treatment methods have the potential to be evaluated within the context of a post-conditioning hormesis treatment methodology, thereby permitting them to be rigorously evaluated within an experimental and detailed dose response framework. Given the controversy that has surrounded homeopathy in modern biomedical domains, it is necessary to indicate that we are making no starting assumption about whether homeopathy is efficacious. Instead, we explore the possibilities that there can be components of homeopathy

that have a scientific explanation and whether that explanation is related to the phenomenon of hormesis.

HOMEOPATHIC PRINCIPLES

Homeopathy is a therapeutic medical system developed in the 1800's designed to cure its patients by enhancing the healing/recovery process following the onset of illness/harm. It claims to do this by giving patients small doses of substances that are said to stimulate a healing response. In some cases, the doses of these administered substances are measurable and in some cases they are not. Homeopathic medicines (often called "remedies") are administered to patients that induce symptoms of the disease displayed by the patient. Homeopathic medical treatments were reported by its originator, Samuel Hahnemann, to cause primary and secondary symptoms, with the primary symptoms occurring first, followed by secondary symptoms.[7] The secondary symptoms were also characterized as being "opposite" to the primary symptoms. While Hahnemann at first thought that both types of responses were symptoms of the drug treatment, he subsequently concluded that the secondary symptoms were the response of the organism to the drug. That is, the primary symptoms were the actual effects of the drug on the organism while the secondary symptoms were reparative processes. In the parlance of 19th century homeopathy, secondary responses were commonly referred to as a response of the "vital force" of the body, a term that was not meant to be mystical, but was used by opponents of homeopathy[8] to link it with certain non-scientific philosophical perspectives (see Calabrese, 2005[9] for an historical review). In practice Hahnemann and his school of homeopathic thought held that primary symptoms are the responses to be recorded in "provings", that is, the testing of homeopathic drugs. When a medicine is administered whose primary symptoms are identical to those of the disease, the patient's response to the treatment, that is, the secondary symptoms, will be "opposite" of the disease symptoms and are part of the body's healing process.

During his practice Hahnemann observed that the administration of drugs in large doses often enhanced the patient's discomfort, that is, primary symptoms.[7] By reducing drug dosage he diminished the magnitude of the primary symptoms. However, the secondary symptoms were not believed to be affected by the lowered dose. Since the healing process is a function of the secondary symptoms, this discovery provided a theoretical foundation for the development of strategies for dose size reduction that was differentially adopted in homeopathic medical practice. Even from quite early after the development of homeopathy there was a conflict between the high and low dilution subgroups within the broader field of homeopathy.[10-12] Ideally, the goal would be to find the "optimal" dose, that is, the lowest dose that induces the secondary response.

HUGO SCHULZ, HOMEOPATHY AND HORMESIS - THEIR INTERACTION

The hormetic dose-response describes how biological systems respond to chemical/physical stressors as noted earlier. The homeopathic treatment is intended to manipulate the normal healing process and to enhance and/or accelerate it. In practical terms, the medical goal of homeopathy is the restoration of health and to prevent the occurrence of relapses.[7] Homeopathy relates to hormesis by trying to enhance the restorative process, that is, the compensatory response to damage. It does not address the issue of overcompensation, but only an acceleration of the repair process. Thus, the hormetic overcompensation, that is, the effect for which hormesis is most noted, is not the principal or even a secondary focus of homeopathy. However, significant debates arose within early homeopathic theory and discourse as to what action (restorative or overcompensation) was most important in homeopathy, with Hahnemann being an advocate for the former.[10-12]

The induction of hormetic responses has been overwhelmingly studied in experimental settings that do not relate to the clinical framework in which treatments are given to ill patients who have already displayed primary and probably secondary symptoms.[9] The research of Schulz, and essentially all studies dealing explicitly with the concept of hormesis, have not addressed hypotheses related to accelerating repair processes after primary and secondary symptoms were induced by drug treat-

ment. Thus, the biological findings of research on hormesis have not found a significant clinical extension. Is such an extension possible?

It is known that injury can be reduced and tissue repair accelerated if a low dose of toxic agent is given BEFORE exposure to an injury inducing exposure of toxic chemicals or radiation.[13] It does so in a manner that the dose response of the conditioning or adapting dose follows a hormetic-biphasic pattern. This phenomenon has been widely observed and referred to by several terms including adaptive response, pre-conditioning, and auto/hetero-protection. Since the low dose exposure is administered prior to the high dose induced injury it does not relate to the normal clinical situation in which treatment is sought following the onset of illness/injury.

Dose-time response relationship experiments may provide some insight on the earlier observations of Hahnemann on how the secondary response is related to the intensity of the primary symptoms. Branham[3] addressed the quantitative features of compensatory (i.e., "secondary") responses of yeast to 16 chemical disinfectants. The stimulatory (i.e., overcompensation) responses in all cases were under two-fold of the control value, suggesting a generally similar quantitative response pattern. There was a tendency for those cases with relatively modest damage ($\leq$ 30% decrease below control) to recover to control values more quickly than when initial damage was relatively high ($\geq$ 50% decrease below control). This indicates that the time to restore the homeostatic condition is related to the magnitude of the induced damage.

The present paper sought to better clarify and correct the long-standing, but mistaken, belief in the homeopathic medical tradition that the research of Schulz[2] provided a scientific foundation of homeopathy.[14] The research of Schulz was not designed to address the critical hypothesis of homeopathy concerning whether its medical treatments or other stressor agents can accelerate repair processes after a prior induced damage. Therefore, it cannot be used to support the scientific foundations of homeopathy. Where the work of Schulz[2] might have significance to homeopathy, and this is more convincingly shown in the replication study of Branham,[3] is the clarification of the quantitative relationship between dose-induced primary and secondary responses. Yet even the study of Branham is not directly related to the homeopathic hypothesis. The present analysis therefore cannot provide support for a toxicologically based justification for a dose lowering strategy in homeopathy since the experiments (e.g., Schulz) are not directly relevant to the hypothesis needed to be tested. Furthermore, the hormetic hypothesis does not have evaluative relevance to other, fundamental assumptions (i.e., like cures like, infinitesimal doses) upon which the field of homeopathy is based.

PRE AND POST-CONDITIONING HORMESIS MODELS OF HOMEOPATHY

During the 1990's research was initiated to address the limitations of the previously discussed study design of Schulz[2] to assess the homeopathic theory which involves the stimulation of biological defenses and repair processes using medicinal agents that follow the similar ("like cures like") principle (see Van Wijk and Wiegant, 1997[15] for a description of this research program). The general approach involved the development of a model experimental system which mimicked clinical homeopathic treatment. Under normal circumstances an ill patient would be treated with a medicinal preparation that is prescribed consistent with the similar principle and the dosing strategy. In the case of the simulated model system, it was proposed that low doses of stressor agents would be applied to disturbed cell cultures. While the disturbed (i.e., stressed) cell culture has the potential to simulate the "ill patient", the low dose stressor agents could represent the homeopathic treatment. Amongst the biological systems to measure stress responses (e.g., various heat shock protein syntheses and survival) were Reuber H35 hepatoma cells, a cell line in which a large number of hepatocyte characteristics remain.[16] In their studies, the researchers typically administered a moderate heat shock which affected a rapid increase in the synthesis of various heat shock proteins (Hsps), leading to the development of thermo-tolerance and enhanced capacity to survive a subsequent lethal temperature stress. Subsequent administration of a range of chemical

stressors such as As, Cd, Cu, Hg, Pb, menedine, and diethyldithiocarbamate (ddtc) at concentrations that did not affect untreated cells were made. However, at their respective "no effect" concentrations each agent enhanced the synthesis of Hsps and stimulated development of thermo-tolerance when administered to cells pretreated with the modest heat shock. More specifically, the "no effect" treatments of each agent, which were given after the "modest" heat stress, enhanced survival in cell cultures given a subsequent near lethal heat exposure eight hours after the modest heat stress exposure. The magnitude of the enhanced survival ranged from 11-65% for the chemical treatments and 95% for the heat stress.

The authors argued that these findings were in partial agreement with the concept of hormesis since a low dose of agents displayed an adaptive response. However, they noted that hormetic effects are usually studied in non-disturbed/non-stressed models. They also argued that hormetic effects are non-specific whereas they concluded there was some degree of agent-specific response in their data. Their findings were therefore consistent with the homeopathic concept in which disturbed/stressed systems administered "no effect" doses of agents with the more successful agents inducing responses more like the "disturbing" agent, that is, modest heat response.

DISCUSSION

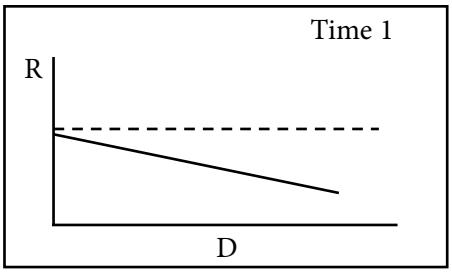
The methodology used by van Wijk and colleagues is conceptually similar to post-conditioning, but they went beyond the usual attempts to simply demonstrate the phenomenon, by examining the pattern of Hsps induction for each stressor and finding it predictive of high dose protection. This is a broadly recognized phenomenon in which a low dose of a stressor agent administered after a more massive exposure to the stressor agent reduces the toxicity of the massive exposure. The degree of damage reduction, based on post-conditioning, is similar to that reported with preconditioning. A recent paper Calabrese et al.[13] indicated that both pre and post-conditioning were specific types of hormesis since conditioning doses typically display a biphasic dose response optimization with similar quantitative estimates to responses in the hormesis database for large numbers of agents, endpoints and biological models.[9] Based on this assessment it is proposed that the medical practice of homeopathy, when evaluated in a manner consistent with the methodological framework presented by van Wijk and colleagues, would represent a special case of post-conditioning hormesis. However, the actual methodology employed in these studies is even more complicated than only post-conditioning, but involving both pre and post-conditioning components.

Homeopaths commonly use low doses in a prophylactic manner; however, there is little data or models for studying such pre-conditioning adaptogenic responses in either normal or dysfunctional systems. One set of experiments worth examining that compares hormesis and homeopathy are those of Bellavite.[17] Like van Wijk, Bellavite has conducted extensive theoretical and experimental modeling exploring the way adaptogenic responses within complex systems might be therapeutic effects using extended models of pre-conditioning.[17-20]

The post-conditioning-like research of Van Wijk and Wiegant[15] and the pre-conditioning work of Bellevite[17-20] represent model systems that have potential relevance to assess homeopathic concepts. The research designs clearly fall into the general realm of a pre and post-conditioning hormesis framework. Numerous experiments by these groups[17-24] and others indicate that below threshold doses, when administered before or after a more massive insult, may enhance the adaptive capacity of damaged/intoxicated biological models. While these studies have been limited with respect to dose range evaluation (and do not apply to the "ultra-high" dilutions used in some forms of homeopathy[a] it is likely that there will be a dose response optima reflective of the hormetic-like biphasic dose response as amply demonstrated within these pre and post-conditioning experimental protocols. If this is the case, then these experiments may provide a theoretical and practical means to define the relationship of homeopathy not only to hormesis but more broadly to modern biomedical and clinical sciences as well.

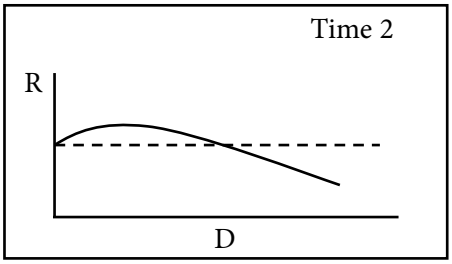
Figure 1. Hormetic dose-time-response. Modest overcompensation following a disruption in homeostasis. (See review by Calabrese, 2001). (R = Response; D-> = Increasing Dose; ----=Control Response).

A1



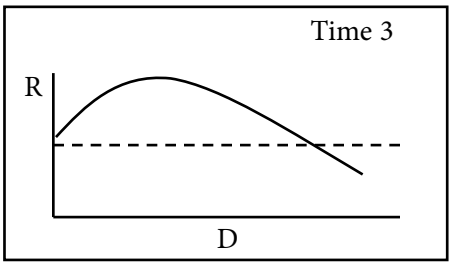
Note the dose-dependent toxicity, consistent with a linear dose response.

A2



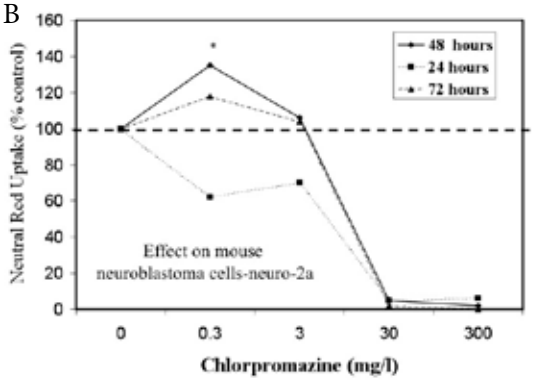
Note that an initial compensatory response is evident with a slight overcompensation response at low dose.

A3



Note that the dose response at Time 3 is similar to the quantitative features of the hormetic dose response.

B



The dose response is shown at three time points. Initially (at 24 hr) there is evidence of toxicity, followed by the compensatory response[26] (see reference 6 for numerous examples of overcompensation stimulation).

ACKNOWLEDGMENTS:

Effort sponsored by the Air Force Office of Scientific Research, Air Force Material Command, USAF, under grant number FA9550-07-1-0248. The U.S. Government is authorized to reproduce and distribute for governmental purposes notwithstanding any copyright notation thereon. The views and conclusions contained herein are those of the authors and should not be interpreted as necessarily representing the official policies or endorsement, either expressed or implied, of the Air Force Office of Scientific Research or the U.S. Government.

FOOTNOTES

[a]Some forms of homeopathy claim that clinical and biological effects occur when dilutions are made beyond Avogardro's number. Clearly these are not hormetic effects unless the recent hypothesis of Anick and Ives that silica contamination from the walls of glass vials is producing hormetic-like effects at low and measureable doses.[25]

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HORMESIS AND ITS RELATIONSHIP WITH HOMEOPATHY

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ABSTRACT

Homeopathy is an ancient and complex therapeutic method that is rediscovering its scientific foundations. Hormesis is a frequently observed phenomenon that has been rigorously reported with precise dose-response curves. The therapeutic method based on the principle of "like cures like" should not be confused with hormesis, which has several different implications from those of homeopathy. Yet, because both these approaches to nature and medicine are very broad in scope, they do end up having some points of contact. Thus the well-established and consolidated field of hormesis can help cast light, through its ideas and research methods, on the possible mechanisms of action of remedies in ultra-low doses.

INTRODUCTION

Homeopathy and hormesis are two different concepts, because the former is a therapeutic method whereas the latter is a phenomenon inferred from careful observation of nature, and described through mathematical curves. Therefore, hormesis is not homeopathy, nor does it provide the "explanation" for it. Homeopathy (as a therapeutic method) and hormesis (as a natural phenomenon) must each construct their own general theories and find their own specific mechanisms and explanations. Nevertheless, as well illustrated by Calabrese and Jonas[1], there exist various points of contact which can suggest common avenues for future research. Often, the progress of science is inspired by analogies which reveal similarities between distinct systems: pre-existing knowledge of a – generally simpler – reference system (so called archetype) is used to construct working hypotheses for extending knowledge of a less well-understood – and generally more complex – system.

HORMESIS

Science is an instrument for knowledge whose language is prevailingly quantitative and which has the specific episteme of creating "symbols" for describing and interpreting reality. Consequently, the success of scientific theories is often also bound up with the symbols that they create and the words that they use, such as "atom", "receptor", "antibody", "cytokines", "fractal", "apoptosis", etc. These words evoke in our minds figures (symbols) that help us to think about the "true" objects and phenomena of nature. Hormesis is a clear concept, with a simple definition, that is thus useful for describing a phenomenon that occurs in both natural reality and in laboratory.[1] The major symbols it employs are an upside-down U shaped dose-response curve and a rebound curve over time; it makes extensive use of mathematical and statistical analysis. The word ("hormesis") and the symbols ("reverse U" and time-courses) are effectively and widely used for describing the relationship between living things (cells, tissues, entire organisms) and the chemical-physical world with which they come into contact. This approach applies to an extremely wide range of significant phenomena – from medicine to ecology – so that hormesis has justifiably gained increasing importance.

Hormesis highlights certain phenomena (or facts, or experimental evidence), but does not itself constitute any sort of explanatory theory, least of all for home-

[1] Hormesis is a dose-response phenomenon characterized by a low dose stimulation and a high dose inhibition. More accurately, it is a dose-time-response relationship in which there is an initial dose dependent toxicity response followed by a compensatory/rebound response, such that at low doses the response becomes greater than the original background state or control group value (Calabrese and Jonas[1]).

opathy. Each example of hormetic curve requires its own explanatory theory, which identifies the "mechanism" accounting for this behaviour of matter and living things, in the specific circumstances where it is observed. Precisely for this reason, the concept of "hormesis" is highly "fertile" ground for stimulating research on phenomena ranging from gene expression to oncogenic risk, and from microbiology to radiation pollution: each of these fields can be explained through one or more mechanisms, which are today being explored with ever greater detail and thoroughness: transduction of extracellular signals into intracellular messages, molecular, cellular and tissue defence and repair systems, control of cell growth and cell death, neurobiology. These involve the formation of complex control networks - based on multiple and interacting feedback loops - which have the ability to adapt cell behaviour in extremely varied ways, making it possible to trace the self-regulatory mechanisms of the functions activated by different doses of the same substance.

This raises two issues with respect to hormesis, connected with its presumed significance and universality. For what concerns its significance, there is a tendency to regard hormesis as a "compensatory" response to stress. Now, this may doubtless be true in many cases, but it does not constitute a rule. In some situations, hormesis may have explanations, causes and functions other than "compensation": for example, at the cell level a hormetic phenomenon could be due to the fact that a cell may have two types of receptors (with high and low affinity) for the same substance; these two receptors could be coupled with transduction pathways that are respectively excitatory and inhibitory; likewise the differences in timing might not be due to "compensatory" or "rebound" mechanisms, but rather to the different speeds with which the two responses are activated: if the positive response to small doses involves protein synthesis or cell replication, it could easily be slower than, and hence occur subsequently to, the more rapid effect of inhibitory blockage. In this case, we cannot properly speak of compensation, but only of a simple overlap between two distinct pharmacological phenomena in the dose-response and time-course curves.

For what concerns the universality of the phenomenon, it must be said that, though hormesis is very common, it is not observed unfailingly in every case. In our experimental work, especially in the laboratory, we have always borne in mind the possibility of "discovering" hormetic phenomena in the behaviour of human leukocytes subjected to the most diverse treatments, and found it to often occur, under certain conditions, but not indiscriminately. For example, podophyllotoxin is a toxic substance that inhibits the function of granulocytes in high doses, but stimulates it when used in low doses (such as those contained in homeopathic products); however this stimulation does not occur when the cell function is activated with phorbol-myristate acetate; in this case, we observe only an inhibitory effect, without the hormetic effect [2]. Much more recently, we have described how quercetin, a natural substance found in foods, dose-dependently inhibits the function of basophils stimulated with anti-IgE antibodies (which simulate the allergic mechanism), without a hormetic effect; on the other hand, hormesis is observed, very clearly, when the cells are stimulated with bacterial peptides, and in that case the low doses of quercetin have an effect that enhances the response to the peptides [3]. This difference in the presence or absence of hormetic responses may have a distinct role in the pharmacologic regulation of inflammatory phenomena. Note that this consideration on the universality of scientific evidence also applies to homeopathy, and in particular to the principle of "similars", which is not true always and in every case but only under certain particular conditions. [4]

One limitation of the possible application of hormesis to homeopathic theories is the fact that hormesis – by definition – concerns substances which in high doses have a toxic effect. In reality, though, there exist substances with regulatory activity whose "toxicity", at least of direct type, is difficult to demonstrate. Consider for example neuromediators, hormones, cytokines, and common mineral salts. Homeopathy does not use only diluted "poisons", but also substances with modulating, regulatory action that are not direct toxins. What is more, in our experience (but also in the literature) there have been cases where a substance was found to have a stimulatory effect on a particular cell function

when used in high doses, but an inhibitory effect when tested in low doses [5-8]. This "reverse hormesis" is difficult to explain within a framework that assumes toxic effects of high doses, unless we consider the toxic effects to be the potential consequences on the entire organism of the substance in high doses. For example, in the cases we have cited, diclofenac stimulated platelets but, probably precisely for this reason, could cause damage to the stomach mucosal circulation; bacterial peptides in high doses stimulated the vitality of leukocytes, but this could lead to an excess production of toxic oxygen radicals, etc.

Hormesis has had the great merit of disproving, with incontrovertible evidence, the belief that cause and effect must always be linearly related. This confutation of an old idea has, in its turn, provoked a domino-like collapse of many other mistaken theories, such as the claim of "conventional" pharmacology that there must be a linear relation between the dose of a drug and its clinical effect. If hormesis were to be "taken seriously" by the world of pharmacology, it would call into question the interpretation of pharmacokinetic curves: in fact, the concentration in the blood of any drug administered orally will be extremely low during its initial stages of absorption and in its final phases of excretion. During those times, if a hormetic phenomenon were to occur, the effect of the drug would be exactly the opposite of that intended. One strong indication that this is a very concrete possibility, even for very common drugs, is provided by the work of Doutremepuich et al. on aspirin. [9-14]. It is worth mentioning, in this regard, that these authors observed the phenomenon of effect inversion with "ultra low" doses and also with "homeopathic" doses.

In thus confuting the accepted theories, hormesis reaches its peak of "unconventionality" but also of "scientificity", because science is "strongest" precisely when it demonstrates - on the strength of evidence - that previously held views were limited or incorrect. Interestingly, at this stage of its development, the role of hormesis is historically comparable to the challenges levelled against conventional medicine by the homeopathic tradition. [15]

HOMEOPATHY

Homeopathy is a method devised to find remedies for curing patients at a time (late 1700s, early 1800s) when therapeutic methods were only empirical and for the most part ineffective. The books on the history of medicine often neglect to mention that, in the historical period when it arose, homeopathy constituted the most "scientific" pharmacological approach discovered until then, for the following reasons: a) It was based on observations that were initially empirical, but which gave rise to a pharmacological theory (or rather, a general reference-principle): that of "like cures like"; this principle, irrespective of whether or not it was correct, gave medicine a pharmacological theory to work out. b) This general principle, which existed already in Hippocrates, became, after Hahnemann, a method for designing clinical tests on volunteers (relatives, students) which enormously expanded the body of knowledge of the 19th century pharmacopoeia; by way of example, we note that nitroglycerin was tested as a drug by Hering in 1849, while its use in allopathic medicine began some 30 years later [16]. c) It was such tests, rather than abstract philosophical ideas, that revealed new properties of remedies in very low doses or even in high dilutions/dynamizations, thereby extending the possibilities for their use in hitherto undreamt of dosages.

Homeopathy thus should have had no need to demonstrate its "scientificity". Yet, in practice, it ran into serious problems because the economic implications of the new discoveries, and a lack of "diplomacy" on the part of Hahnemann, shifted the debate from the realm of scientific research to that of a power struggle implicating the very survival of entire fields of medicine and pharmacy.[2] Unfortunately, even homeopathic practitioners

[2] In this connection we note that the battle is far from over, as we ourselves have experienced on sending rigorously scientific papers to various pharmacology journals, with the response that they refused even to consider the work (that is to say not even submitting it for peer review), not because of any methodological objections, but merely because the subject was homeopathy. Homeopathy is not considered a part of pharmacology, despite the fact that professional physicians prescribe homeopathic remedies, and that these are purchased and used by the public: one example of how ideology (or economic interests) often stifle science and even common sense.

themselves are not fully aware of the scientific basis of their discipline. The words and symbols ("similarity", "dynamization", "potency", "miasm", "vital force") have remained the same for two hundred years, but homeopathic physicians have been "content" with these original forms, which have always enabled them to survive and practice their profession. Another factor aiding the survival of homeopathy was that the competing fields of "clinical" medicine did not have a great deal of scientific content at their disposal, and medicine had great difficulty (and still does) incorporating science into its conceptual arsenal.

Homeopathic medical science has never ceased constructing theories and working hypotheses about its basic principles, which are essentially three: the law of similia, the law of minimum dose, and the "holistic" treatment of the patient. These principles can in their turn be subdivided into many other points and subpoints, as typically occurs in any scientific theory: moving from the general to the particular.

THE HOMEOPATHIC "SIMILE"

To compare the fundamental principle of homeopathy with hormesis, we need to carefully define the working concepts. We agree with Calabrese and Jonas [1] in drawing a distinction between homeopathic "similars" and hormesis. In homeopathy, "like cures like" essentially means that a particular substance (in small doses or high dilutions, it doesn't matter here which) can cure a disease whose symptomatology in the patient is similar to that caused by the same substance in tests on healthy subjects. This founding-idea (theory) has been repeatedly tested in the experiments of homeopathic practitioners and has held up over time, albeit not in a sufficiently "strong" manner to convince the entire world of medicine.[3]

[3] It should also be specified that the homeopathic pharmacopeia has, during the course of two centuries, spawned many diverse branches which include a purely "clinical" use of the remedies: in short, if a remedy demonstrates therapeutic efficacy on a particular *disease*, it can be used again as a "nosological" indication for that disease. In practice, this is very close to the concept of evidence-based medicine, even though the approaches suggested for proving homeopathy are often different from the conventional "double-blinded randomized clinical trial" [17].

The theory of homeopathic "simile" is starting to be explained from a mechanistic standpoint, consistently with modern immunological and biological theories, with which it is partly in agreement and partly in opposition (as is also hormesis, in a different field). For example, today it is possible to explain--or very closely approach an explanation of -- how a substance (e.g. bee poison) that causes pathological symptoms in healthy subjects (pain, inflammation) can cure similar pathological symptoms in subjects allergic to bee poison. The substance is administered sublingually to the allergic subject, in extremely small doses, and induces immunological tolerance by activating the counter-regulatory mechanisms of the lymphocytes. Much has also been written about so-called "paradoxical pharmacology", according to which it is possible to exploit the "pathogenic" properties of drugs (determined from the pathological symptoms which they provoke in healthy subjects during phase 1 studies) for curing diseases that exhibit precisely those symptoms [18-20]. Though this is not overtly called "homeopathy", it is nevertheless, unintentionally, homeopathy: it is simply a question of agreeing on the words and symbols that are used.

It is also possible to design laboratory studies to test the following "homeopathic" idea: a given substance causes an effect (for example stimulation) on resting cells or animals, but the same substance causes an opposite effect (for example inhibition) when tested on cells or animals that have been previously stressed or disturbed in some way. The idea – originally described as the "Wilder rule" – has been tested in many studies of experimental physiology, cell biology and molecular biology [21]. Obviously, each individual model makes it possible to highlight a small aspect of such a general rule, thereby outlining some possible mechanisms. At the basis of it all, though, is the sensitizing/desensitizing of the receptors and the signal transduction pathways, caused by the pathology itself, which makes the stressed subject or system more sensitive and responsive to certain treatments and less so to others, even to the point of response inversion due to homeodynamic adaptations of the reactivity and the effector systems, typical of living organisms.

Another important mechanism which would explain the different actions on healthy subjects and patients is that the remedies may target only diseased tissues and not healthy tissues. [22]

DOSES

The homeopathic Materia Medica includes many poisons, and was compiled from observations of accidental poisoning cases, and through experiments on volunteers. The latter, obviously, had to be conducted with doses capable of provoking "symptoms" which, though disagreeable (but at times also agreeable, as can happen with some drugs), would not however cause serious damage to the subjects. So it came naturally to reduce the doses to the minimum amount that was able to provoke symptoms (in the healthy subject) and to cure them (in the patient). It should be added that the effects of any drug are multifarious, so that when subjects are asked what symptoms they experienced after taking it, they will probably (or certainly, according to homeopathic experience) report effects involving many aspects of physiology and psychology. It is also likely that, as the dose is reduced and the most noticeable "toxic" symptoms which affect all subjects are abated, other more specific symptoms, affecting more "sensitive" subjects, may remain or even emerge. This is why the homeopathic Materia Medica comprises such a "wealth" of symptoms, observed and meticulously described. We shall not debate here whether such methods are correct and statistically validated - a question not relevant for our present purposes, though it "weighs" greatly on the quality of the medical prescriptions based on such reports.

Therefore, for what concerns dosages, it is obvious that overly high doses of any poison will have pathogenic effects, whereas low doses may have slightly pathogenic effects (liable to cause unpleasant symptoms) or pleasant or therapeutic effects, depending on the similitude we have discussed above. Certainly, this aspect has many conceptual analogies with hormesis. Nevertheless, we disagree with the general classification of these pharmacological effects as "compensatory", i.e. responses to damage induced by a high dose. In our view, the discussion on "primary" (direct) and "secondary" (indirect) effects – introduced by Hahnemann himself to try to construct a theory of the remedy – is somewhat contrived, and in any case unnecessary for clarifying the point of therapeutic effects of low doses of poisons. In practice, biological systems react in a unitary manner, so that these two types of effects of a remedy or toxic substance can only be artificially separated. To give a very simple example, consider the case of a single protein: if a chemical substance binds to an amino acid, the entire protein alters its secondary and tertiary folding, or may form a complex with another protein etc. In this case it is not possible to say whether the effect of the chemical substance is direct or indirect. Therefore, regardless of the theorised two types of actions of the remedy, the general working principle remains the same: use the lowest possible dosages, which appears to be in line with modern, intelligent pharmacology. The more "specific" and "targeted" a remedy is (i.e. directed to highly sensitive receiving systems), the lower will be its effective dose. A list of experiments where reproducible biological effects induced by compounds used in the concentration range of attomoles (10^{-18} moles/litre) or even zeptomoles (10^{-21} moles/litre) was previously reported [23].

DILUTIONS/DYNAMIZATIONS[4]

One fortunate circumstance for homeopathy, historically, was that although Avogadro's principle was formulated in the early decades of the 19th century, the precise computation of the number of molecules in a gram-mole was published by Loschmidt only in 1865 (in fact today we speak of the Avogadro-Loschmidt constant). This meant that there was no "scientific" objection to the use of ultra-diluted substances, and homeopathy was not theoretically destroyed, at least not in those years. The worst period came between the 19th and 20th centuries when, also thanks to the

[4] Logically speaking, we can speak of a "dose" of a given substance only when that substance is present, and therefore when its concentration is higher than 10^{-24} moles/litre (approximate Avogadro limit). Beyond this limit we can no longer speak of doses or concentrations, because a substance may not be present in an amount that is less than zero. That is why in homeopathy it is more correct to speak of "dilutions/dynamizations", which can be logically pushed beyond the Avogadro limit (corresponding to the 12^{th} centesimal or 24^{th} decimal dilution, starting from a solution of 1 mole/litre).

discovery of chemotherapeutics, homeopathy was brought to bay and reduced to a shadow of its former self. Today, in the computer era, we understand a great deal more about the physics of condensed matter, and in particular of aqueous solutions containing gases, silica and ions (pure water does not exist), and this enables us to consider (at least as a hypothesis) various potential mechanisms by which "non molecular" information might be incorporated into ultra-diluted solutions and transmitted to an organism [24;25]. We shall not here discuss this controversial question. However, to clarify the relation with hormesis, it is sufficient to note that many experiments conducted thus far on highly diluted solutions tend to show that the biological action of a given substance does not change direction when going from "very low dose" to "highly diluted-dynamized solution". The most frequently described instance is the modulation of the function of basophil granulocytes by histamine, which is apparent both with low and unquestionably molecular dilutions (for example 2CH which corresponds to 10^{-4} moles/litre) and with high dilutions (for example 16CH which corresponds, theoretically, to 10^{-32} moles/litre) [26;27]. The response of the living system to very high dilutions/dynamizations, when it can be observed, generally has the same direction as that to low (sub-toxic) dilutions containing ponderal, molecular doses of the substance to which the system itself is chemically sensitive. Considering histamine, the "inversion of effects" may be conceived only by comparing the effect of this substance in the connective tissue (where at high doses it behaves as irritating, pro-inflammatory compound) with the effect on basophils (where it suppresses by internal feed-back the release of histamine, thus behaving as anti-inflammatory compound). There are, however, discrepancies between different laboratories on this point regarding the inversion of biological effects in highly diluted solutions [28-30], so that the question cannot be considered resolved.

We agree with Calabrese and Jonas [1] when they maintain that, in the "high-dilution" field, it is difficult to find points of contact between homeopathy and hormesis: the "classical" hormetic curves are in fact correctly and completely constructed only for "doses", - that is to say concentrations - from "zero" (no effect, taken as control) upward, whereas homeopathy, as we have seen, also uses dilutions where theoretically there are no molecules of the purported active principles inside. In this second case, a "common ground" between homeopathy and hormesis could be found only if we accept the possibility of "supra-molecular" states of organization of the solvent, influencing the cell responses independently of the concentration of the solute. At present, this hypothesis is widely speculative, but we cannot rule out that studies based on the hormesis model may, in future, be extended to ultra-diluted solutions, should it become possible to determine the "concentration" of any clusters, nanobubbles, nanoparticles or the like. Most probably, given that hormesis, too, is a phenomenon that seeks wider application in medicine, it would find fertile ground in the growing diffusion of homeopathy worldwide.

CONCLUSIONS

To conclude, is there space for hormesis within homeopathic theories? It would be helpful if this were true, because hormesis is a very robust phenomenon that also lends itself to formulating models and working hypotheses. Homeopathy has need for demonstrable facts and methodological rigour; it also needs to rid itself of the reputation of being unscientific. Calabrese and Jonas [1] suggest that "certain forms of homeopathic treatment methods have the potential to be evaluated within the context of a post-conditioning hormesis treatment methodology, thereby permitting them to be rigorously evaluated within an experimental and detailed dose response framework." We fully concur with this view. If homeopathic remedies could be studied according to this approach (at least those made with low dilutions of substances) it would be a major step forward for homeopathy and medicine. This would however imply enormous research effort, because it would require plotting the dose-response curves of homeopathic remedies: first in pre-clinical studies (on animal models), and then on humans (first healthy volunteers and then patients), and in conditions under which sensitivity is highly likely to vary greatly between individuals (which would require using large groups of patients to obtain statistically valid results). It is therefore foreseeable that the points of con-

tact between homeopathy and hormesis will, at least for some time, remain within the sphere of laboratory research - which in itself is already significant - though without ruling out more advanced forms of collaboration and the possibility of finding more concrete implications in medicine, or of studying the mechanisms of actions of many other compounds or poisons.

In the final analysis, therefore: long live hormesis, and long live homeopathy, which are two different things but able to positively interact, as always happens when there is genuine scientific interest. We can find many points of contact because the reality is vaster than our symbols, and because our old and new words can proliferate and recombine to continually form new phrases. All this bearing in mind that the ultimate aim of all efforts in medicine is, as written at the start of the Hahnemann's Organon, to care for patients and, where possible, to cure them.

ACKNOWLEDGEMENTS

The study was supported by grants from Verona University and from Laboratories Boiron s.r.l., Milano, I.

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HOMEOPATHY: CLARIFYING ITS RELATIONSHIP TO HORMESIS

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ABSTRACT

The significant connection between homeopathy and hormesis is stressed out, but it is also suggested that this connection is limited. Basic differences can be found in the range of concentrations in which hormesis is operative and in the lack of peculiar methodologies for drug preparations. In the meantime the clinical application of hormesis does not need any categorization typical of homeopathic therapies and can provide a large set of useful experimental results to be used for improving homeopathy itself.

In this contribution the connections between the homeopathic therapy and the hormesis phenomenon are explored. This subject is not new and has raised several debates. The approach proposed by the authors is simple and clear and it deserves consideration. Notwithstanding its crystal clear character, I think that the arguments are not able to remove the unsolved questions unless the medical community forces herself to reconsider his own basic *tenets*. In fact there is no doubt that the problem involves an intrinsic dichotomy because of the different conceptual roots defining the operational contexts of the two subjects. If this dichotomy is not removed, the subject of the contribution remains undefined too.

The experimental data show that the hormetic dose response phenomenon is a quite general result which follows the interaction of a living organism with a xenobiotic perturbation. The stimulatory or inhibitory character of the response is not only qualitatively but also quantitatively related to the amount of the perturbing agent. Although at macroscopic level it is rather difficult to rationalize the cascade of biological processes following these interactions, the ambivalent or biphasic character of the responses opens the way to a new perspective of the pharmacological approaches to be used in the medical therapies. In other words, the experimental data suggest that the application of the hormesis in medical clinics is justifiable. This means that the medical doctor may find convenient to exploit in turn the stimulatory or inhibitory properties of the same xenobiotic interaction in order to modulate the behaviour of a living organism. Therefore the wide development of microdoses pharmacology is strongly required. A further support to this statement is given by the consideration that the studies of Van Wijk and Wiegant, cited by the authors, show that the hormetic dose response is the resultant of the perturbed cells system and that this answer follows a general paradigm. Studies we are carrying out at the University of Florence support these results at molecular level, showing how the up- and down-regulation of several genes is xenobiotic concentration dependent. This represents again a full justification for the clinical application of the hormesis phenomenon.

The above data sets can be consistent with the existence of a connection between hormesis and homeopathy, but, how stressed by the authors, this connection is limited. It is true that this should be associated with pre- and post-conditioning considerations, as it is made in this contribution. It should be mentioned the fact that hormesis does not require any special procedure for the preparation of the xenobiotic, like the so-called dynamization, and it is believed to be effective only in a concentration range consistent with the quantization of matter. Indeed up to date no hormetic effects have been detected for ultra low-doses of xenobiotics, a subject which is patently contrasting with the pillars of traditional hahnemannian postulates. But, what it is more important, it should be also stressed the difference between a well defined and reproducible experimental approach, as provided by hormesis studies, and the formulation of a mind-conditioning categorization model, as the one adopted in the medical practice of homeopathy and based on somewhat foggy euristic consider-

ations. This does not want to mean that the homeopathic therapeutic tenets must be cancelled. It only means that hormesis and homeopathy cannot be considered synonymous, but that the awareness of the hormetic concept in the mainstream medical thought can provide a more appropriate background for the keplerian revolution of the pharmacology in this century. Of course, as a personal feeling, I hope that this approach would improve the development of the whole body of the homeopathic knowledge.

DOES HOMEOPATHY HAVE ANYTHING TO CONTRIBUTE TO HORMESIS?

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ABSTRACT

Homeopathy is the best known medical analogue of hormesis, others include hormoligosis and paradoxical pharmacology. Homeopathy is based on the concept Similia similibus curentur ('Let like be cured by like'); the exploitation of secondary effects of drugs, the body's reaction rather than the primary pharmacological action.

The most controversial aspect of homeopathy is its use of 'ultramolecular' dilutions in which a single molecule of the starting substance is unlikely to be present. Classical pharmacological actions in-vivo have been reported with dilutions as high as 10^{-22}mol/L, but homeopathic medicines may be far more dilute than this.

There is growing biological evidence including independent reproduction that in-vivo effects may occur at such dilutions. In a systematic review 73% of experiments showed an effect with ultramolecular dilutions including 68% of high quality experiments. Physical and physico-chemical work suggests that homeopathic preparations contain stable ordered supramolecular structures, gas nanobubbles and dissolved silicates may be involved.

Homeopathy may contribute to the generalizability and reproducibility of hormesis effects. It also raises the question of the threshold of hormesis effects.

INTRODUCTION

Calabrese and Jonas' dispassionate and scholarly exploration of the relationship between homeopathy and hormesis is a welcome contribution to clarifying the scientific issues surrounding homeopathy. Unlike some other recent contributions, it generates more light than heat or smoke. Too frequently, throughout its history, debates around homeopathy have degenerated into heated and rhetorical dialogues of the deaf, and the debate around homeopathy is currently passing through one of its periodic maxima. Indeed Calabrese has argued elsewhere that its association with homeopathy has been a major factor in the exclusion of the hormesis from scientific discourse.[1] Views from within the homeopathic community on the relationship between homeopathy and hormesis vary, some believe that the two are distinct[2] while others point out crucial similarities.[3] Hormesis and homeopathy have been compared and contrasted by Luckey.[4]

HORMESIS AND ITS MEDICAL ANALOGUES

Hormesis is the paradoxical, stimulatory or beneficial action of toxins, and as such its therapeutic potential is obvious. Several medical and pharmacological analogues of hormesis propose the therapeutic use of such effects. Homeopathy is the best known, but other analogues include hormoligosis[5] and paradoxical pharmacology.[6,7] Drug rebound effects are closely related to temporal hormesis, although their application is mostly in the area of safety rather than therapeutics per se[8].

Homeopathy was founded in 1796 (in a curious zeitgeist, this was the same year as Jenner first vaccinated against smallpox), by the German physician Samuel Hahnemann, based on the concept Similia similibus curentur ('Let like be cured by like'). This he opposed to the allopathic or enantiopathic method (based on 'contraria contrariis': opposites oppose). Calabrese and Jonas use the term allopathic loosely to refer to all conventional medicine, but in fact conventional medicine also employs other concepts of drug action, for instance that of differential toxicity, the underlying rationale for antibiotics and cytotoxic agents.

The observation of secondary, paradoxical effects of drugs, the body's reaction as opposed to the drug's primary pharmacological action, was seminal to Hahnemann's thought. As he put it: 'Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed primary action. Although a product of the medicinal and vital powers conjointly, it is principally due to the former power. To its action our vital force endeavors to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of secondary action or counteraction.' [9]

Although Hahhnemann was the first to systematically base therapeutics on secondary action, the idea was far from new; there are many earlier references including Paracelsus' famous dictum from the early 16th century 'All substances are poisons, there is none which is not a poison, it is but the dose which distinguishes a poison from a remedy'. References to these contradictory concepts of the relationship between disease and its treatment can be found in the Hippocratic corpus (circa 450BCE), for instance: 'Diseases are cured by opposites; for every disease there is something proper; so, for what is warm by nature, but sickened by cold, there is something to warm it up, and so on. This is another way: by *similar* (homoia) means a disease arises and by administering similar things health is restored from sickness; for instance the same which causes strangury that wasn't there before, when it is there, will make it stop. Likewise coughing arises, like strangury, and it stops by the same things.'[10] Similar concepts can be found in Asian traditional medical systems.

The common thread linking hormesis to its medical and pharmacological analogues, including homeopathy, is that all involve the secondary paradoxical effects of drugs and toxins in biological systems as a function of dose or time.

THE PROBLEM OF ULTRAMOLECULAR DILUTIONS

Homeopathy includes other concepts, and of these by far the most controversial is its use of dilutions in which a single molecule of the starting substance is unlikely to be present. Such dilutions are referred to as 'ultramolecular' or ultra low dilutions (ULD), or BRAN (Beyond the Reciprocal of Avogadro's Number). These dilutions are prepared by a process known as potentization which involves repeated dilutions, usually in steps of 1:10 (denoted x or d) or 1:100 (denoted c), with succussion (vigorous shaking) at each step. Count Amadeo Avogadro proposed in 1811 that the volume of a gas is proportional to the number of atoms or molecules regardless of the nature of the gas. The value of Avogadro's constant, the number of particles (atoms or molecules) in a mole of a pure substance is 6.022×10^{23}. The inescapable implication is that dilutions above 23x or 12c (corresponding to dilutions of 10^{-23} and 10^{-24} respectively) are very unlikely to contain a molecule of the starting substance. In fact the 'molecular threshold' is usually crossed before this dilution, depending on factors including initial concentration, molecular weight etc. Classical pharmacological actions in-vivo (defined as interaction between pharmacologically active molecules and receptors) have been reported with dilutions as high as 10^{-22}mol/L and frequently at dilutions of 10^{-17} - 10^{-18} .[11] It is important to remember that many homeopathic medicines are of lower dilution, at which the original substance is materially present.

Nevertheless this a fundamental problem, although Calabrese and Jonas politely skirt around it. I, however, will address it head on, and not only because it is unavoidable, but also because it poses an important question to hormesis, in the form of its old opponent, threshold. I was introduced to hormesis by ARD Stebbings' classic 1982 review paper Hormesis: The Stimulation of Growth by Low Levels of Inhibitors[12]. The centrepiece of this paper is a series of figures plotting hormetic effects in a wide range of biosystems, showing the characteristic 'hockey stick' curve. I was struck by the fact that in the graphs there is a

break in the x (dose) axis, close to its origin, indicating that one should not intrapolate, presuming that the dose response curve returns to zero in a linear fashion below the lowest measured dose. As a homeopath I was also aware that this area is very large if one includes homeopathic dilutions, and that there is more research in the area than many assume. For instance a meta-analysis led by Prof Claudia Witt of the Charité University Medical Centre, Berlin evaluated the quality and results of in-vitro biological experiments with homeopathic dilutions. Quality was assessed by a modified SAPEH score. 75 publications were found of which 33% were replications. 73% showed an effect with ultramolecular dilutions including 68% of high quality experiments. 73% of replication experiments were also positive. [13]

BIOLOGICAL MODELS

The most frequent model is basophils, used in 42% of experiments. One series comprises 17 experiments on the inhibition of basophil activation by high dilutions of histamine. It spans over 25 years and includes multi-centre and independent replications. There has been steady refinement of the method, including improved markers and the introduction of flow cytometry.[14 15] There is a consistent peak at 16c (10^{-32}), well into the ultramolecular range. The effect is hormetic, in the same sense as doses of histamine in the low molecular range but opposite (at least at the whole organism level) to that of higher doses of histamine. There is also insight into possible mechanisms of action, for instance the response is highly specific to histamine; it is not induced by the structural analogue histidine, and it appears to be mediated by H2 receptor-mediated inhibition of basophil activation.

Another cellular system which has been the subject of repeated experiments over a long period is the effect of ultramolecular dilutions of aspirin on blood clotting. The effect is again hormetic: ultramolecular dilutions promote clotting, the reverse of substantial doses.[16,17] Recent work with 'knock-out' mice suggests that the effect is due to inhibition of COX-2 mediated PGI_2 production in vascular endothelium.[18]

The most robust whole animal model is the effect of thyroxine on the rate of metamorphosis of frogs. Again the effect is hormetic: in substantial dose thyroxine accelerates metamorphosis, it has the reverse effect in ultramolecular dilution.[19] This effect has been reproduced in multi-centre experiments[20] and by independent workers with different species of frog.[21]

Many other biological model experiments in homeopathy have been conducted. The HomBRex Database on Fundamental Homeopathy Research is maintained by the Carstens Foundation.[22] It contains details of approximately 1300 such experiments using intact organisms or parts of organisms.

The close relationship between homeopathy and hormesis is illustrated by the work of Wiegant's group at the University of Utrecht, Netherlands. They studied the specificity of low dose responses in cultured rat hepatoma cells using a post-conditioning protocol. The cells were subjected to heat shock followed by low doses of chemical toxins. The greater the similarity (as measured by the pattern of heat shock protein production) between the two stresses, the greater the cell survival.[23] Several of the toxins used are homeopathic medicines, and these experiments can be construed equally as investigating post-conditioning hormesis or the similarity principle of homeopathy.

DOES HORMESIS HAVE A THRESHOLD?

These findings are provocative for hormesis, since they raise the issue of Threshold. Where does the threshold for hormetic effects lie? Calabrese and Jonas generally avoid the issue of ultramolecular dilutions, although in a footnote they state these are not hormetic effects. I question this. There is nothing in the definition of hormesis which states that it is concerned only with low concentrations of chemicals, as radiation hormesis proves. There is an unspoken assumption that chemical hormetic effects have a threshold somewhere above the Avogadro Limit, although perhaps not far above. But this is only an assumption (albeit a deep-seated one), and it is challenged by the experimental results cited above.

These findings pose a challenge in terms of understanding any putative mechanism of action. Homeopathic medicines are prepared in water-alcohol mixtures and most attention has focussed on so-called water memory effects induced by the preparation process. It is suggested that hydrogen bond mediated structural or coherence effects, and dissolved atmospheric gases or silicates from the glassware may play a role.

MEMORY OF WATER

Experiments using a range of standard physical and physico-chemical methods have reported structural anomalies in water prepared according to the homeopathic method. Methods include low temperature thermoluminesence, flux calorimetry, conductometry, pHmetry Raman and Ultra-Violet–Visible (UV–VIS) spectroscopy and Nuclear Magnetic resonance (NMR).

Low temperature thermoluminesence involves freezing water to the temperature of liquid nitrogen, irradiating it, then warming it, whereupon it emits a characteristic glow. The 'signature' of lithium is detectable in ultramolecular lithium chloride by this method[24]. This result has been independently verified.[25] The effect appears to be dependent on the atmosphere in which the dilution is conducted, the effect is more marked with dilutions prepared in an oxygen atmosphere and less so in dilutions prepared under reduced pressure, compared to normal atmosphere.[26]

NMR results have varied, depending on the parameters measured.[27,28] But when 20MHz T1 and T2 water proton NMR relaxation rates are measured, homeopathic dilutions of histamine are distinguishable from solvents up to ultramolecular levels. The effect is attributed to stable supramolecular structures, involving nanobubbles of atmospheric gases and highly ordered water around them. It is deleted by heating.[29,30] Recent work of which Jonas is a coauthor suggests that silicates dissolved from glassware may also be involved in water memory effects: silicates at concentrations too low to have direct in vivo effects greatly enhance the stability of enzymes and might influence in vitro biological assays reporting homeopathic effects.[31]

Work from the Materials Research Institute of Pennsylvania State University shows that ultradilute homeopathic medicines can be distinguished from controls and each other by Raman and Ultra-Violet–Visible (UV–VIS) spectroscopy[32,33]. These effects may be due to epitaxy, the transfer of information, not material, from the surface of one material, usually solid, to another, usually liquid. Semiconductor manufacturing often uses epitaxial growth to generate specific types of microtransistors.

Elia's group at the University of Naples has published series of papers investigating physico-chemical properties of ultramolecular dilutions. Using standard methods, they have detected, anomalies of specific conductivity, heat of mixing and other parameters.[34,35,36] They interpret these findings as reflecting the presence of extended, ordered dynamics involving liquid water molecules, in the form of dissipative structures, in such dilutions. Dissipative structures, described by the Nobel Laureate Ilya Prigogine, are complex, self-organising systems, far from thermodynamic equilibrium.[37] Within a dissipative structure there is long-range interaction between particles, and they exchange energy and matter with their environment. Examples include cyclones, lasers and living organisms

CRITICISMS OF WATER MEMORY

The claim that water can 'remember' substances with which it has been in contact, and that such 'memory' is mediated by hydrogen bonds has been criticised, mostly on theoretical grounds.[38] Such arguments mostly involve the short duration of individual hydrogen bonds in liquid water (about a picosecond).

The short half life of individual hydrogen bonds, however, does not imply that the larger scale structure of water must change on the same time scale. Such arguments ignore the fact that the behavior of a large population of water molecules may be retained even if that of individual molecules is constantly changing: a wave can cross an ocean, remaining a wave although its molecular content is continuously changing; on a smaller scale, cation hydrates with particular structure are commonly

described even though the individual water molecules making up such structures have very brief residence times (microseconds).[2] Most researchers in the area believe that the water memory effects concerned in homeopathy are of mesocale (of the order of a micron, as opposed to the microscale of individual molecules or the megascale of ocean waves).

Evidence against long lived water clusters is mostly based on computer simulations but these cover only nanoseconds of simulated time. Such short periods are insufficient to show longer temporal relationships, for example those produced by oscillating reactions. They also involve relatively few water molecules (100–1000), small (nanometre) dimensions, insufficient to show mesoscale effects, and are based on models of the water molecule whose predictions correspond poorly to the real properties of water.

In any case certain water memory effects are well established and uncontroversial: for instance the formation of clathrate hydrates from aqueous solutions whereby frozen clathrates within the solution, when subsequently melted, predispose to more rapid clathrate formation.[39] This is explained by the presence of nanobubbles, extended chain silicates or induced clathrate initiators.[40]

WHAT CAN HOMEOPATHY CONTRIBUTE?

The generalizability and reproducibility of hormesis is disputed, and it has been alleged to have few practical applications.[41,42]

Does homeopathy have anything to contribute here? On a purely pragmatic level, homeopathy is a practical implementation of a concept analogous to hormesis which, although controversial, has withstood the test of time and is remarkably popular and widespread.

Homeopathy takes a clear view on how hormetic responses can be induced and exploited to therapeutic effect. Homeopathic practice pays great attention to whole person characteristics and individual idiosyncracy and sensitivity. Modern research emphasises the highly specific nature of homeopathic responses, the importance of sensitivity or presensitisation and of whole system responses.

Modern theoretical work in homeopathy has considered the conditions under which whole system recovery, driven by 'vital reaction' occurs, is impaired or enhanced, drawing on complexity theory, particularly non-linearity, self-organization and dynamicity[43,44], and network theory.[45] Such work focuses on the dynamics of homeopathic effects, including issues such as specificity, sensitivity to the initial state of the system, whole system responses and physiological attractors. Improved understanding of these will enhance the generalizability, reproducibility and practical exploitation of hormesis and its medical analogues.

Finally homeopathy poses a fundamental question for hormesis: what is the threshold for hormetic effects?

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MIASMAS, GERMS, HOMEOPATHY AND HORMESIS: COMMENTARY ON THE RELATIONSHIP BETWEEN HOMEOPATHY AND HORMESIS

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ABSTRACT

Is hormesis related to homeopathy? Despite the superficial similarity of the low dose of the applied stimulus, there are compelling reasons for maintaining hormesis and homeopathy as unrelated. Homeopathy originated in the medical knowledge vacuum of the 19th century, prior to the acceptance of the germ/gene bases of disease. Homeopathy was never grounded on empirical scientific evidence. Hormesis, on the other hand, has always been an empirical science, involving properly controlled experiments. Hormesis is a concept in toxicology that involves biphasic dose responses in biological systems, wherein low doses of stressors can have beneficial effects, and higher doses have harmful effects. Hormesis, as it applies to toxicology, is a necessary and useful concept describing adaptive organismic responses to applied stressors. Conversely, homeopathy is a medical doctrine based on the erroneous belief that substances which cause the symptoms of a disorder will cure the disorder when given to patients in small doses. To suggest that homeopathy is a form of post-exposure conditioning hormesis assumes that homeopathic practitioners employed the scientific method with measurable experimental endpoints and proper controls, and that their "provings" had actually determined the correct compound, at the correct dose, required to cure a disorder. Because many homeopathic preparations are diluted to a point where none of the starting solutes would likely remain, the idea of a beneficial or harmful hormetic dose becomes moot. Without supporting scientific evidence for the efficacy or purported mechanisms of homeopathy, the term hormesis should not be linked with it in any way.

INTRODUCTION: MIASMAS AND GERMS

Homeopathy is one of the few European medical doctrines of the 19th century that has survived, and even thrived, into the 21st century, despite a lack of supporting scientific evidence. Prior to the application of the scientific method to the study and treatment of human diseases, numerous medical doctrines competed for favor throughout Europe during the Renaissance. These were based on popular concepts of the time, ranging from perturbations of a vital force, to imbalances of good and bad bodily humors. Up until this time, one of the world's most widely accepted medical treatises was the medical encyclopedia Al-Qanun fi al-Tibb, or the Qanun, completed in 1025 by the Arabic scientist and doctor Ibn Sīnā. The full work was translated into the multi-volume Latin version, "The Canon of Medicine" in the 12th century[1]. Sīnā was the first to document the transmissible nature of infectious diseases, and established the method of quarantining contagious patients to prevent the spread of disease. Despite the broad scope and authority of this work, the nature of disease causing agents remained unknown such that many competing Western theories were put forward to explain the substance and mode of transmission of human diseases. Many of these theories were based on unscientific concepts, or concepts improperly borrowed from chemistry or physics. These competing theories of disease causation and treatment

vied for popularity throughout the 16th and 17th centuries, and continued to draw adherents up through the 18th and 19th centuries.

Science was progressing rapidly in Europe in the early 1800's, particularly physics and chemistry, which were much further advanced than biology and medicine. European medical practice was primitive and factionalized, and there was no consensus on disease causation, or treatments. Simultaneously, urban life became more crowded, and public sanitation became a growing problem in cities such as London and Paris. Overcrowding and sanitation issues caused many disease outbreaks throughout Europe in the 1800's prior to understanding of the transmissible nature of many diseases, and the implementation of urban sanitation and public health. This was the intellectual and social milieu within which homeopathy emerged in Europe, and so it may be useful to recall the theoretical divisions between 19th century doctors who adhered to the miasma theory of transmissible disease with those supporting the germ theory of disease using cholera epidemics in London as an example. The first clear formulation of the germ theory of disease may be from 1840, when the eminent German anatomist and pathologist Friedrich Gustav Jakob Henle published "On Miasmata and Contagia". This work distinguished various diseases based on whether they followed the miasmatic (airborne) or contagion (water/contact/proximity) method of transmission. Henle defined "contagion" as a living, organic entity ("contagia animate") capable of independent existence, or parasitic existence within a diseased body.

The miasma theory was the main competing theory of disease, and was much more widely accepted than the germ theory at the time that cholera epidemics spread throughout Europe between 1832 and 1866. The miasma theory posited that foul smelling vapors from decomposing mater mixed with elements of the air to produce "miasmata", or poisonous gases that led to various diseases. Those who adhered to the miasmatic theory of human disease believed that cholera, typhoid and other diseases were not transmitted from person to person, but rather were caused by foul odors from decomposing mater, and were transmitted by air. These were known at the time as "anticontagionists", and included many physicians of England's General Board of Health, and the Committee for Scientific Inquiries[2]. Physicians and scientists who believed in the person-to-person transmissible nature of diseases such as cholera were known as "contagionists".

By the mid 1800's the concept of miasmas was intimately entwined with theories of fermentation. It was observed that multiple types of fermentation existed, so-called spirituous fermentation in the making of wine or beer, acetic fermentation in the case of vinegar formation, lactic fermentation in the case of the souring of milk, and putrification in the case of rotting meat or eggs. However, the great majority of scientists and physicians of the day did not believe that fermentation or decomposition had any relationship to microscopic organisms, which were well known ever since the invention of the microscope in the 1600s. The science of chemistry was evolving rapidly in the mid 1800's, and many preeminent scientists of the day, including Antoine Lavoisier, considered all types of fermentation to be chemical, rather than biological processes. The miasma theory of disease incorporated these ideas, and it was postulated that some type of "ferment" of decomposing matter created the etiological agent, which was airborne. The British Board of Health concluded that three convergent factors were involved in the cholera epidemic, including stagnant air due to lack of wind, high barometric pressure, and high river water temperature at night. These conditions were thought to produce nocturnal emanations of clouds of miasmatic vapors from the Thames river that, when catalyzed by the cholera ferment in the atmosphere, induced cholera in epidemic proportions in the local population.

John Snow, a British physician and member of the Cholera Inquiry Committee, was not convinced by the miasma theory of disease, and instead believed that fecal matter from cholera patients was getting into the water, and that this was spreading the disease. During the so-called "Golden Square" cholera outbreak in South London in September of 1854, the death toll rose quickly, and public officials scrambled to identify the source of the outbreak. The General Board of Health favored the idea

of transmission by air, via a miasmatic-ferment mechanism. Experiments were done to determine if any substance could be filtered from the air in the district to determine what form the ferment might take. They found mold spores, fungus and dust, but nothing that could be associated with the pathogenic substance of cholera. Snow used a different approach and employed statistics to show that the outbreak correlated with the use of a particular local water pump, the "Broad Street pump" in the center of the South London neighborhood where the outbreak occurred. Water samples from the pump did not show particularly high levels of microorganisms, or any other possible etiological agent. However, based on Snow's work, the pump handle was eventually removed, and residents began using other nearby water pumps. Later, after the outbreak had subsided, an examination of the cesspool at 40 Broad Street showed that it was only inches away from the broken lining of the Broad Street pump that had been dispensing sewage tainted water and causing the local outbreak.

While it is clear now that Snow's statistical calculations were imperfect, and his data were incomplete, he nonetheless laid some of the foundations for modern medical epidemiology[3,4]. But at the time, Snow's conclusions were rejected by the British Board of Health, and the Committee for Scientific Inquiries. However, the controversy centered on the mode of transmission, and theories about what specific agent spread the disease, not over the root cause, which was seen by both sides of the debate to be a lack of public sanitation. The anticontagionists believed that decomposing matter was acted upon by a chemical reaction (cholera ferment) to cause a miasmatic cloud that led to the disease in those who inhaled enough of the vapors. The contagionists believed that certain living microscopic organisms (often called "vibriones" at the time) present in the water were responsible for the outbreaks. Miasma and contagion theories both eventually concentrated attention on pubic sanitation, and therefore their efforts tended to merge[2]. This trend continued as evidence mounted throughout the second half of the 19th century in favor of the germ theory of transmissible disease. What started as a move toward improved public and hospital sanitation by proponents of both the miasma theory and germ theory eventually helped open the way for modern medicine, and it's scientific approach to understanding disease causation. Homeopathy, on the other hand, never adopted the scientific method, but proceeded instead with the method of so called "provings", which from the outset was defined as the antithesis of "standard medical practice".

HOMEOPATHY

C.F.S. Hahnemann coined the term "allopathy" in 1842 to differentiate the established practice of medicine from homeopathy, his alternate system of therapy. Homeopathy was based on the concept that diseases can be treated with minute doses of compounds thought to produce the same symptoms in healthy people as the disease itself. Hahnemann believed that nothing could be known of the underlying nature of a disease, because disease does not arise from biological causes, but rather from a perturbation of the "vital spirit."[5]. Based on personal experience with Peruvian tree bark containing quinine, Hahnemann experienced malaria-like symptoms, thus leading to his formulation of the basic principle of homeopathy, that "like shall be cured by like". Allopathy, in Hahnemann's simplistic view, treated symptoms with drugs having actions opposing the symptoms of disease. Hahnemann defined the "law of similars" as the central principle of homeopathy. Drugs or toxins that were known to cause symptoms similar to a particular disease were given to patients in extremely diluted form[6]. This was said to induce a restorative process in the body that would counteract the effects of the disorder being treated. Allopathy was a term and concept invented by Hahnemann that did not properly characterize medical practice, and created a false dichotomy between two terms invented by Hahnemann himself: "allopathy" and "homeopathy"[7]. Hahnenann's concept of allopathy was a mischaracterization from the outset, a straw man against which he could pit homeopathy.

Hahnemann described the actions of dilute remedies as inducing two different sets of symptoms, primary symptoms that are similar to those of the disease to be treated, and secondary symptoms that are opposite, and act to

counter the effects of the disease. The idea that compounds that induce specific primary and counteracting secondary responses in the body would act to enhance natural healing is attractive, because it seems to be an intuitively sensible notion. However, compounds that cause fever do not necessarily combat infection, and compounds that cause stomach ache do not necessarily relieve indigestion. Giving heart disease patients low doses of compounds that cause heart problems would not induce a healing response. The basic premise of the law of similars, while appealing as a story, does not prove true in practice. Indeed, the theoretical underpinnings of homeopathy have never been demonstrated empirically. The final major tenet of homeopathy is that it is purported to be a system for stimulating the healing process, but this claim also was hypothetical, rather than being derived empirically.

HORMESIS

Classical hormesis can be defined as a non-linear, homeostatic biological response to toxins, or stressors such as ionizing radiation, that is biphasic in the sense that opposite effects are seen when different exposure levels are applied[8-10]. With low dose exposure to some toxins, or certain types of radiation, a biological response is observed that is opposite to the effects seen with high doses. The data plot as inverted U or J shaped curves that contact the control value at two points. Biological systems tend to respond to stressors at multiple levels, including molecular, cellular and tissue, with interacting negative and positive feedback mechanisms that compensate for perturbations. The concept of hormesis is particularly relevant to toxicologists and radiation biologists, who are concerned with determining detrimental exposure levels for environmental or industrial toxins and radiation. Expanding the concept of hormesis to all non-linear biological responses, such as the effects of nutrients, psychological stress or exercise[10,11] would greatly dilute the usefulness of the term. Many biological responses are non-linear, so expanding the use of term hormesis to include all normal physiological responses in cells, organs or populations enlarges the scope of the term so far as to make it meaningless. Hormesis is a more powerful and useful concept when it is used to refer to special cases of adaptive biochemistry or physiology where low dose exogenous toxins or radiation exposure increases the expression of defense and repair mechanisms that protect against higher level exposures.

"Post-exposure conditioning hormesis" refers to cases where exposure to a low-dose stressor such as a toxin after a higher dose exposure can lead to an adaptive response that reduces the overall detrimental effects of the initial high level exposure[12]. Reports of this type of hormetic response are less common than so-called "conditioning hormesis", where the lower, adaptive dose occurs before the higher, harmful dose. Because post-exposure conditioning hormesis occurs when the adaptive low dose exposure follows the high dose harmful exposure, it bears some superficial similarity to homeopathy. However, there are both logical and practical reasons why this analogy does not hold up under scrutiny.

IS THERE A CONNECTION BETWEEN HOMEOPATHY AND HORMESIS?

Homeopathy is said to work by the law of similars, which states that low doses of compounds (often toxins) that cause specific pathological symptoms (e.g., fever) will counteract diseases that manifest with the same symptoms. This notion has never been demonstrated experimentally, and is not accepted by modern science. Homeopathy further states that the primary symptoms of a remedy are similar to the symptoms of the disorder being treated, but the secondary symptoms act to counter the disease state. Therefore, if homeopathy had some kernel of biological validity that had lured researchers to pursue the field, then homeopathy should have rigorously examined the proper doses of various toxins required to elicit measurable secondary effects. This would have been the pursuit of post-exposure conditioning hormesis meticulously performed by the scientific method.

There is a logical inconsistency in the idea that homeopathy could be acting as a form of post-exposure conditioning hormesis. Post-exposure conditioning hormesis

involves using the same toxin or stressor in the initial harmful exposure, and in the subsequent post-exposure adaptive dose given at a much lower concentration. If this concept is being applied directly to low-dose homeopathy, then it presupposes that the illness or disorder being treated by homeopathy was caused by some agent that was similar or identical to the one the homeopath is using as a post-exposure conditioning agent. Homeopaths usually treat patients who have ailments of unknown cause or etiology. Therefore, it would be impossible to determine the correct "stressor" (post-exposure conditioning agent) that needed to be utilized simply based on the patients symptoms, by applying the "law of similars". Homeopathy was developed under the simplistic and erroneous concept that the "secondary" effects of a remedy would always counteract any illness that resembled the "primary" effects of the remedy. This bears no similarity to the concept of hormesis where the dose of the toxin or stressor is the most critical factor in determining if the system responds positively by adaptation, or is damaged by excess levels of the toxin or stressor.

Most importantly, if homeopathy were related to post-exposure conditioning hormesis, then it would be expected that numerous homeopathic practitioners would have been able to clinically or experimentally determine the correct low dose of a compound capable of inducing a protective, hormetic response. This would have been the norm in homeopathic practice. If this notion was true, and the researchers and practitioners studying homeopathy over the last 200 years had been competent experimentalists, they would have spent their time carefully mapping out protective hormetic doses of many of the toxins they still employ today in ultra-dilute form. They would have been able to show that particular toxins were useful in specific disease states due to specific, adaptive (secondary) responses that could be measured clinically or experimentally. Instead, there is no agreement among homeopaths on specific treatments, or doses for homeopathic preparations for any particular disorder. In fact, many homeopaths have reported that reducing the dose of preparations to levels that are far beyond those being capable of inducing any significant biological response makes them "more potent", thus rendering the notion of dose irrelevant. If homeopaths and researchers investigating homeopathy had discovered post-exposure conditioning hormesis, they would never have come to the conclusion that reducing the dose of the remedy effectively to zero increased effectiveness in producing reparatory secondary effects. Hahnemann and his followers invented the principles of homeopathy, rather than determining the principles of hormesis.

Hormesis is a very useful concept in biological toxicology that deals with low dose, non-linear biological responses to harmful agents. Homeopathy is a 19th century medical doctrine that is not based on scientific principles or investigations. Connecting homeopathy with hormesis may be an attractive story, but it is unproductive to attempt to redeem any portion of Hahnemann's views in light of modern biology. It is best to let go of the law of similars, as we have let go of miasmas, ether, entelechy and phlogiston. Investigators studying hormetic biological responses have no need to expand this concept to assimilate any aspect of homeopathy.

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HORMESIS AND HOMEOPATHY: BRIDGE OVER TROUBLED WATERS

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> ***"The opposite of a correct statement is a false statement. But the opposite of a profound truth may well be another profound truth."***
>
> - NIELS BOHR

ABSTRACT

Homeopathy is an empirical method of treatment. Hormesis, while stemming from within the rationalist tradition, has yet to be explained according to current pharmacological theory. Both share in common sub-threshold doses of toxic substances and an initial semi-toxicological insult followed by a greater compensatory (or healing) response. We question whether the differences between these fields may be amenable to scientific research.

We identify five cardinal differences between homeopathy and hormesis: 1) Hormesis is a universal phenomenon, while homeopathy is highly specific; 2) Hormesis uses only measurable quantities of compounds, as opposed to homeopathy, which frequently administers medicines at dilutions far beyond the material range; 3) Preparation of hormetic solutions follows standard laboratory procedure, while homeopathy requires a sequential series of dilutions, each followed by vigorous shaking ("succussion"); 4) The effects of hormesis are moderate and temporary, while homeopathy claims curative and permanent responses; 5) Hormesis is a lab phenomenon observed primarily in healthy organisms, whereas homeopathy is a mode of treatment administered primarily to ailing individuals. We believe that all five of these differences are amenable to scientific investigation, and suggest comparing succussed to non-succussed diluted solutions as an optimal first evaluation. We conclude that while certain differences exist between hormesis and homeopathy, hormesis may in fact be a subset of homeopathy.

INTRODUCTION

Empiricism is an epistemological theory which argues that knowledge can only be acquired via the senses, i.e. from experience. According to empiricism, all hypotheses and theories must be tested in the context of human experience and observations. Knowledge is therefore *"a posteriori"*, while *"a priori"* knowledge - steming from reasoning alone - cannot exist. Rationalism is the diametric opposite of this approach, maintaining that true knowledge can only be gleamed through reason *("a priori")*. Rationalism sets out cognitively consistent premises and attempts, through a logical sequence, to deduce every possible realm of knowledge. These rival epistemological schools have been vying for the mind of science since ancient Greece, reaching a crescendo during the "Age of Enlightenment" of the 17th and 18th centuries [1].

Homeopathy is a branch of complementary and alternative medicine (CAM) that treats a disease specifically by the administration of minute doses of a remedy that would in larger amounts produce symptoms in healthy individuals (also termed the "law of similars")[2]. Hormesis is a "dose-time-response relationship in which an initial dose-dependent toxicity response is followed by a compensatory/rebound response [3]. Both fields share in common the administration of sub-threshold doses of potential toxins, and both profess an initial semi-toxicological insult followed by a greater compensatory or healing response. In the current issue of this journal, Calabrese and Jonas evaluate the relationship between hormesis and homeopathy and suggest an experimental framework for evaluating certain aspects of the latter [3]. We wish to further examine the relationship between these modalities and suggest a research plan to further investigate their relationship.

Homeopathy was founded by Dr. Samuel Hahnemann in Germany at the end of the 18th century. In his magnum opus, "The Organon of the Healing Art", Hahnemann states that "only the (morbid) symptoms… as perceived externally by means of the senses" can be the true indication as to what is to be cured [4]. Furthermore, Hahnemann maintains that the healing power of medicines could "never be discovered by a mere effort of reason" [5], and that "only by experience of the phenomena it displays when acting on the state of health of man" [5] could medicines express their therapeutic range of action. Thus, from its inception, homeopathy has been a purely empiricist form of medicine, with respect to both its diagnostic methodology and mode of treatment.

Nearly a century later, a new science was to emerge independently: hormesis. Hormesis - a lab phenomenon in which low-but-material doses of known toxins induce an initial toxic action and a secondary rebound reaction - was first observed by Schulz in 1888 [5], and formed the basis of the Arndt-Schulz law. The namesakes were a conventional pharmacologist and physician, but they realized that their observation had no grounding in the known pharmacological laws of the time. A comment by Schulz led to the association of hormesis with homeopathy and presaged its fall into disrepute. Alfred J. Clark, a leading 20th century pharmacologist, played upon this speculative association, and succeeded in delegitimizing hormesis for the better part of a century [7]. If homeopathy is the quintessential empirical medicine, hormesis' epistemological foundations are more questionable. Hormesis was born out of an empirical observation adopted by a cadre of rationalist investigators, only to be rejected by that school, for political more than scientific reasons [7]. Its mechanism remains illusive.

To the homeopathically-trained ear, the hormetic dose-time relationship rings a familiar bell. In the original homeopathic manifesto, Hahnemann describes the primary action of "artificial morbific agents" on a healthy body, followed by a secondary reaction ("counter-reaction", or "curative action") produced by the body's defense mechanisms [8] An example of this phenomenon can be observed by placing one's hand in a bowl of ice water. The hand will feel cold (primary action). However, upon removing the hand from the water, the hand will experience heat and redness, direct evidence of the body's secondary (curative) reaction to the external, primary "insult". Additionally, both homeopathy and hormesis identify biological activity at doses below pharmacologically recognized thresholds. Therefore, the search for common ground between homeopathy and hormesis remains intriguing.

In its quest for legitimacy, hormetic researchers have made every effort to distance themselves from association with homeopathy. Homeopathic practitioners, the scientific outcasts of the medical community, have clung to hormesis as a legitimate low-dose soul-mate [9], homeopathy's putative bridge to mainstream medicine. However, a real examination of the possible linkage between these two modalities has never been undertaken. Hormetic researchers have a strong aversion to any possible association with homeopathy, and homeopaths – most lacking formal scientific training – have not had the qualifications. Thus, the association between these two sub-threshold modalities has remained a matter of conjecture.

In their current paper, Calabrese and Jonas [3] suggest that hormetic research models may represent a suitable venue for the investigation of certain aspects of homeopathy. We tend to agree, but wish to broaden the debate. We propose that the association between hormesis and homeopathy *in general* may be amenable to scientific study.

DIFFERENCES BETWEEN HORMESIS AND HOMEOPATHY

Hormesis differs from homeopathy is several cardinal ways:

1. Specificity of Treatment

The first difference between the two treatment paradigms relates to the non-specific nature of the hormetic response, as opposed to the specific response of homeopathy. The hormetic reaction is described as a universally biphasic response which can be found among a

wide range of organisms responding to a wide variety of stimuli. In other words, toxic agents can be used interchangeably in initiating a hormetic reaction. Homeopathy, on the other hand, is highly specific, both with respect to the patient as well as to the chosen remedy. Nearly 3000 homeopathic remedies can be found in the homeopath's pharmacopoeia, from which the classical homeopath must choose an appropriate remedy capable of creating (and thus curing) symptoms similar to those presented by the patient. Homeopathic remedies are not interchangeable.

2. Use of High Dilutions

The second difference between hormesis and homeopathy relates to the dilutions of the substances involved. Both hormesis and homeopathy employ doses below recognized pharmacological thresholds. However, whereas hormetic researchers have restricted their investigations to doses that are low but within the material range, homeopathy does not limit itself to material doses, and frequently administers medicines at dilutions far beyond Avogadro's number. The homeopathic community has historically been split between the "lows" - those employing low dilutions, often within the hormetic range, though individualized to each patient - and the "highs", classical homeopaths who employ concentrations which may start within the material range (such as 10^{-6}) but may reach upward with no theoretical or practical limit, even as high as $10^{-10,000}$. Taking into account Avogadro's number (6.02×10^{23} mol^{-1}), the number of atoms in the world is in the order of 10^{50} [10], with the number of atoms in the known universe estimated at about 10^{79} [11]. Classical homeopathy must therefore part ways with the law of mass-action and the dose-response curve, as well as any other vestiges of the prevailing physical-chemical science. In short, whereas a homeopathic response is anticipated above or below Avogadro's number, hormetic effects remain within the province of the material.

Homeopathy does employ a dose-response relationship of sorts, though its nature is diametrically opposed to that commonly recognized in pharmacology and toxicology. Classical homeopaths claim that the higher a substance is diluted, the more potent (i.e. fundamental, profound, and long-lasting) its effects become. Thus, a patient with a seasonal flu might receive a homeopathic remedy diluted to between 10^{-12} and 10^{-24}, with the hope that this would cure him of his symptoms. At the same time, a patient suffering from dysthymia and heartburn which relate back to painful childhood memories would be a candidate for a remedy diluted to 10^{-60} or even 10^{-400}. The higher dilution of the remedy would be expected to revive these childhood experiences, initially aggravating the heartburn but ultimately "curing" both physical and emotional disturbances. Homeopathy therefore claims a dose-response of sorts, but one very different from that of classical pharmacology.

3. Preparation of Homeopathic Remedies/ Hormetic Compounds

The third difference between homeopathy and hormesis pertains to the manner of preparation of each of their remedies, respectively. The preparation of hormetic solutions appears to be a rather straightforward procedure, albeit precise; familiar and feasible in any basic chemistry lab. In contrast, the preparation of homeopathic remedies is a complex and fundamentally inexplicable process. Though homeopathy's infinitesimal dilutions have become its hallmark, they were not a central pillar of homeopathic philosophy, but rather an afterthought. Hahnemann, when administering material doses of 18^{th} century medicines to his patients according to the law of similars, encountered significant adverse effects. This is understandable, considering that toxic substances such as arsenic, mercury, and nitric acid were the pharmaceuticals of the day. Using a purely empirical trial-and-error methodology, Hahnemann began to dilute his remedies in order to minimize these often perilous reactions. Much to his surprise, he found that highly diluted medicines were as potent or even more so when compared with lower dilutions; at least in relation to the parameters he observed. Thus, the concept of high dilutions appeared only as an afterthought, and not as the central concept it is perceived as today.

For reasons unknown to us, Hahnemann remained dissatisfied with the potency of his high dilutions, and

began shaking ("succussing") them vigorously between the stages of dilution. He found that such activity further increased the potency of the remedy, and succussion was ultimately incorporated into standard homeopathic practice. Homeopathic remedies are prepared by a series of dilutions and succussions, with the mother tincture diluted (by a factor of 10 or 100) and subsequently succussed. This process is repeated again and again; 3, 4 or 6 times for "low" dilutions, 9, 12 or 30 times for middle dilutions, and 200, 1000, or 10,000 times for high dilutions. During the pre-industrial era the highest dilution Hahnemann was able to reach was 10^{-60}**.** With the advent of modern technology and the development of industrial dilution/succussion machines, extremely high dilutions became a simple function of machine time.

4. Duration of Effects

The fourth difference between hormesis and homeopathy relates not to the treatment process but rather to the anticipated outcome. Whereas hormesis remains a laboratory phenomenon, intent on demonstrating the possibility that sub-threshold doses of toxins may generate a compensatory/rebound response, the goal of homeopathy is a practical and clinical one, in which a curative process is attempted by stimulating the "vital force" of the biological system. Thus, while hormesis appears to induce a moderate and temporary effect, homeopathy claims that a successful treatment should be both curative and permanent [12].

5. Timing of Treatment

The final difference between hormesis and homeopathy relates to the timing of treatment, as discussed in Calabrese's paper. Hormesis is typically administered to healthy organisms (pre-conditioning) with the intention of observing the initial and compensatory responses. Homeopathy, on the other hand, is a mode of treatment, i.e. administered generally to ailing individuals. In a laboratory setting involving a standardized insult, this would be termed "post-conditioning". However, the divide along these lines is not sharp. Homeopathic remedies are indeed administered to healthy individuals, in the form of formal homeopathic "provings", i.e. eliciting the therapeutic potential of a given remedy. Hormesis, also, does not limit itself to pre-conditioning experiments, but also may be used in post-conditioning set-ups [3].

SCIENTIFIC COMPARISON

Considering these five differences between hormesis and homeopathy presented above – specificity, degree of dilution, method of preparation, duration of effect and timing – we find that most are amenable to scientific investigation.

Specificity: One could imagine a post-conditioning study comparing a non-specific hormetic toxin with a homeopathic medicine tailored to the specific laboratory insult.

Degree of Dilution: A hormetic model could be repeated, but using the same toxin, diluted to beyond Avogadro's number.

Method of Preparation: Possibly the simplest trial would be to measure strength of effect of a hormetic toxin compared with the same toxin, diluted to the same degree, but succussed homeopathically.

Duration of Effect: This could be used as an outcome measure in the previous comparisons.

Timing: Hormesis and homeopathy would have to be examined on even terms. However a series of studies is conceivable, evaluating the two modalities in various timings (pre- and post-conditioning).

The most extensive database today containing studies in basic scientific research of homeopathy can be found at the Karl & Veronica Carstens Foundation site [13]. Given the differences presented above, it would be interesting to review the existing toxicological homeopathic literature found in this collection. We would not be surprised to find that much of the toxicological research found there which claims to be homeopathic, does not fulfill the criteria discussed above for homeopathy. Rather, they are studies which could very well be attributed to the framework of hormesis.

DISCUSSION

The fundamental differences between hormesis and homeopathy have been relegated to conjecture for more than a century. From the homeopathic perspective this has stemmed from a lack of scientific interest and training. From the hormetic perspective this has been due to an ongoing effort to distance itself from homeopathy. We believe that the time has come to rigorously evaluate the relationship between the two: Are hormesis and homeopathy different expressions of the same basic but as-yet unexplained phenomenon, or are they indeed discreet fields of study and therapy? With this question in mind, we applaud Calabrese and Jonas in venturing out into these testy waters. We believe their suggestions could provide a framework for studying low-dilution post-conditioning homeopathy; however, we would expand that framework to include all aspects of the hormetic-homeopathic relationship.

While we envision research into all five differences suggested above - specificity, degree of dilution, method of preparation, duration of effect and timing - we believe that the easiest place to start would be with investigating the differences between the homeopathic and the hormetic method of preparation of compounds. For this purpose it would be practical to identify a well-established hormetic model, and administer the same noxious agent prepared routinely in the chemistry lab, compared with the same agent prepared using dilution and succussion. This simple model could serve as a starting point in observing the effects of succussion (or lack thereof).

We have, in the past, stated that "Hormesis in not Homeopathy" [14]. However, hormesis may in fact represent a subset of homeopathy. More precisely, hormesis may be a rudimentary form of homeopathy, demonstrating commensurately that diluted substances can induce a compensatory/rebound response while stopping short of refining that principle into a mature therapeutic modality. Both appear to act upon the same "adaptive potential" of the organism, though homeopathy's strategy would appear more individualized and specific. We believe this question is amenable to rationalist scientific investigation. In the meantime, hormetic methodology can, at the very least, offer a rationalist model to study homeopathic effects within the low dose range.

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TESTING THE HORMETIC NATURE OF HOMEOPATHIC INTERVENTIONS THROUGH STRESS RESPONSE PATHWAYS

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SUMMARY

The scientific foundations of hormesis are now well established, and include various biochemical and molecular criteria for testing the hormetic nature of chemicals and other modulators. In order to claim homeopathy as being hormetic, it is therefore essential that, in addition to the hormetic biphasic dose response, homeopathic remedies should also fulfill one or more molecular criteria. Since stress response pathways, such as heat shock response, antioxidative response, autophagic response and unfolded protein response, are integral components of the physiological hormesis, it is important that homeopathic drugs be tested for these pathways if these are to be considered as hormetins, and to cause hormesis.

INTRODUCTION

In the article "Homeopathy - clarifying its relationship to hormesis", Edward Calabrese and Wayne Jonas have critically evaluated the controversial link between homeopathy and hormesis. In this well-balanced article, they have explored the homeopathic principles and have pointed towards what is scientifically acceptable and unacceptable in homeopathic theory. They have analyzed the works of van Wijk and Wiegant and of Bellevite, and find that the experimental design and results clearly fall within the post- and pre-conditioning hormetic framework. They suggest that if these experiments are furthered by dose range evaluation, it is likely that a dose response optima, like the biphasic "hormetic-like" dose response, should be found and that such experiments would lay down a more solid foundation for the relationship of homeopathy not only to hormesis but also to modern medicine in general. However, an important aspect of hormesis that Calabrese and Jonas have only touched upon and needs some detailed discussion is the issue of mechanistic molecular pathways through which hormesis is generally considered to be realized, and which can be the basis for judging whether homeopathy qualifies to be considered as hormetic.

HORMESIS AND STRESS RESPONSE PATHWAYS

One of the requirements for any agent to be called hormetic is that it should act as a stressor by causing a disturbance in homeodynamics at the physiological, cellular or molecular levels.[1,2] A critical component of the homeodynamic (homeostatic) property of living systems is their capacity to respond to stress. In this context, the term "stress" is defined as a signal generated by any physical, chemical or biological factor (stressor), which in a living system initiates a series of biological events that enable it to counteract, adapt and survive.[1,2] If such a stressor finally leads to achieving some biologically beneficial effects under the category physiological hormesis,[3] it is termed as a hormetin.[1,4] Table 1 gives a list of main molecular stress responses (SR) that are integral to the organismic property of homeodynamics, and through which potential hormetins bring about their hormetic effects.[5,6]

Table 1. Major molecular level stress responses.

Response	*Stressors*	*Effectors*
Heat shock response	Heat, heavy metals, antibiotics, protein denaturation	Heat shock proteins, proteasome and other proteases
Unfolded protein response	Unfolded and misfolded proteins in endoplasmic reticulum	Chaperones, co-chaperones
Autophagic response	Food starvation, hypoxia, damaged organelles	Lysosomes
DNA-repair response	Radiation, oxidants, free radicals	DNA-repair enzymes
Antioxidant response	Free radicals, reactive oxygen species, pro-oxidants	Nrf-2, heme-oxygenase, FOXO
Sirtuin response	Energy depletion	Sirtuins
NF-κβ inflammatory response	Pathogens, allergens, damaged macromolecules	cytokines, nitric oxide synthase

Based on the involvement of one or more molecular SR, higher order (cellular, organ level and body level) responses are manifested, which include apoptosis, inflammation, and hyperadrenocorticism leading to increased levels of circulating corticosterones in the body. It should, however, be pointed out that not all pathways of SR respond to every stressor, and although there may be some overlap, generally SR pathways are quite specific. The specificity of the response is mostly determined by the nature of the damage induced by the stressor and the variety of downstream effectors involved. For example, cytoplasmic induction of protein denaturation by heat, heavy metals and antibiotics will initiate the so-called heat shock response (HSR) by inducing the synthesis of heat shock proteins (HSP) followed by the activation of proteasome-mediated protein degradation.[7,8] However, unfolded proteins in the endoplasmic reticulum will induce unfolded protein response (UPR), and will initiate the induction of synthesis of a totally different set of proteins and their downstream effectors.[9,10] Thus, the belief by van Wijk and Wiegant, as mentioned in the article by Calabrese, a hormetic response can carry a certain level of specificity such as that observed in the simulated homeopathic system of van Wijk and Wiegant. [11,12]

Of the above list of SR pathways, the HSR is a universal and primordial response achieved by the activation of the HS transcription factor(s), followed by the preferential synthesis of several HSPs, and is considered to be one of the important markers of ensuing hormesis. Induction of HSP as a molecular marker for hormesis is widely reported in various model systems including insects, nematodes, rodents, and human cells in culture.[1] Therefore, in order to consider homeopathy to be hormetic, it is important to know if homeopathic treatments and doses induce HSR in animal cell cultures and in organisms.

A study carried out for gene expression profiling of mice macrophages following exposure to a homeopathic remedy Canova reported an upregulation of 45 genes and downregulation of 102 genes. The 45 genes upregulated also included the genes for heat-shock proteins HSPA1A (7.14 fold increase) and HSPA1B (5.6 fold increase), and other proteins including metallothioneins and thioredoxin reductase, which are also involved in stress response.[13] Although these studies show an upregulation of HSPs at a transcriptional level, it remains to be seen if this would also be true at the translational level.

Furthermore, pathways involving NF-κB, Nrf2, FOXO, sirtuins and heme-oxygenase (HO) activation, which involve more than one type of stressors and stress signals, including pro-oxidants, free radicals, and reactive oxygen species (ROS) must be evaluated for homeopathic formulations. The study by de Oliviera et al. also shows the upregulation of HO-1 (4.57 fold increase) by

Canova treatment at a transcriptional level.[13] In an earlier study, the same authors had reported that macrophages treated with Canova had increased NAD(P)H oxidase and iNO synthase (iNOS) activities leading to the production of ROS and NO.[14] They had also proposed a mechanism that could involve activation of NF-κB/Rel family. Another study reported the autophagy-stimulatory effects of Canova in mice macrophages.[15] Although it is not difficult to envisage an involvement of the above mentioned pathways as a result of Canova treatment, it would be important to demonstrate the involvement of these pathways using functional genomic and proteomic mapping. Similar studies need to be carried out for other homeopathic drugs to establish any link between hormesis and homeopathy. Furthermore, other cell-lines, especially the normal human healthy cells, should be tested to check the effects of the homeopathic molecules.

CALORIC RESTRICTION: A CASE STUDY IN HORMESIS

An example of the critical evaluation as to whether an intervention is hormetic or not is the case of calorie restriction (CR). Chronic, intermittent or periodic CR brings about a wide range of biological effects in various organisms, including slowing down of aging and extension of lifespan.[16] Several mechanisms have been suggested to explain the multiple biological effects of CR, which include a reduction in the levels of molecular damage due to reduced metabolism, a reduction in body temperature, alteration in the extent cell proliferation and cell death, a decline in responsiveness to hormones, and changes in oncogenic expression leading to reduced carcinogenesis.[17,18] Another mechanism that has been invoked in order to understand and explain the beneficial effects of CR is that of mild stressed-induced hormesis,[19-21] which stimulates maintenance and repair systems (MARS).

An analysis made with respect to deciding whether CR is hormetic or not suggests that there are two phases of CR: an immediate adaptive response through hormesis, and a steady state and life long response in terms of improved MARS.[22] For example, an exposure to CR or nutritional deprivation induces a metabolic shift from the production of ATP through glycolytic pathways to mitochondrial pathways,[23] which then leads to increased respiration, increased production of ROS, and consequent damage to mitochondria, other organelles, and to macromolecules. This sequence of events then leads to compensatory hormetic responses including HSR, autophagy, DNA repair response, and antioxidant responses. Similar rigorous and detailed testing of homeopathic molecules will be required to conclude whether these are hormetic or not. Furthermore, the example of CR also shows that CR-induced hormesis results in an overall improvement in homeodynamics by strengthening the networks of MARS, and by reducing the rate of occurrence and accumulation of macromolecular damage. [6]

In the case of analysing whether homeopathy is hormetic, the gene profiling data by de Oliviera et al.[13] indicate that there is a multifaceted response to the homeopathic drug Canova. However, many components of this response that are upregulated or downregulated as compared to the control have not been functionally characterized yet. Moreover, whether or not these multiple responses together comprise the MARS network remains to be elucidated. In addition, there is almost a complete lack of mechanistic studies on different homeopathic remedies at non-controversial concentrations. Therefore, the conclusions drawn from the works of de Oliviera et al. do not necessarily represent a general phenomenon for all homeopathic preparations. It is important that the effects of homeopathic interventions on cellular and organismic homeodynamics are studied in detail.

Calabrese and Jonas in their article maintain that hormesis cannot provide evaluative relevance to another fundamental assumption of homeopathy, *viz.*, the "similia principle" or 'like cures like'. However, in our opinion, hormesis does have a certain component of 'like cures like'. For example, induction of the synthesis of HSP by mild heat stress "hardens" cells and organisms to tolerate the same or higher level of stress later on by synthesizing even more HSP. Although in this sense hormetic and homeopathic principles may seem

to be similar, it would require much more efforts on the part of the homeopathic research community to scientifically test and establish the relationship using the molecular mechanistic framework and criteria of hormesis.

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POST-CONDITIONING HORMESIS AND THE HOME OPATHIC SIMILIA PRINCIPLE: MOLECULAR ASPECTS

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SUMMARY

Postexposure conditioning, as a part of hormesis, involves the application of a low dose of stress following exposure to a severe stress condition. Depending on whether the low-dose stress is of the same type of stress or is different from the initial high-dose stress causing the diseased state, postconditioning can be classified as homologous or heterologous, respectively. In clinical homeopathy, the same distinction is found between isopathic and homeopathic application of low dose substances. Homeopathy is unique for its Similia principle, which implies that substances causing symptoms in healthy biological systems can be used to treat similar symptoms in diseased biological systems. The evaluation of the Similia principle in an experimental set-up requires the analysis of a complex sequence of "damage-disease-treatment-effect" events. The process of recovery from an insult is then monitored and a possible beneficial effect on this recovery process, upon application of a range of substances in low dose, can subsequently be analyzed using molecular and functional parameters. It is then possible to compare the effect of treatment with the degree of similarity between the diseased state and the effects caused by homologous and/or different heterologous substances. Beneficial effects of postconditioning mild stress conditions have been described in terms of an increase of the synthesis of stress proteins. In this commentary paper we present additional information on this aspect. The experimental data suggest that the beneficial effect of the low dose stress condition used as heterologous postconditioning is related to similarity in molecular stress response.

Key words: Hormesis, Postconditioning, Homeopathy, Similia principle

INTRODUCTION

The phenomenon of hormesis is characterized by the biphasic response to particular doses of stress.[1-3] Pioneer researchers Thomas Luckey [4,5] and Edward Calabrese [6-8] produced accumulating evidence in support of the phenomenon of hormesis. The biphasic dose-response pattern is generally thought to reflect the adaptive nature of biological systems in response to stress. Within the framework of hormesis, different approaches are used to elicit an adaptive response. Commonly, a stimulating low dose of stress is administered which initiates compensatory biological processes that confers a protective effect against exposure to a subsequent severe stress. This phenomenon is known as *preconditioning* hormesis. Less conventional is *postconditioning* hormesis: the administration of a low dose of stress to enhance repair and recovery processes *after* exposure to a more severe stress. Depending on whether the low-dose stress administered during postexposure is of the same type of stress or is different from the initial high-dose stress, postconditioning can be classified as *homologous* (i.e., the subsequent stress is the same as the initial stress) or *heterologous* (i.e., the subsequent stress is not the same as the initial stress).

Reproducible assessment of postconditioning within a clinical framework may be difficult to realize. It is complicated by the narrow window within which the inducing agent initiates protective effects. Outside the therapeutic window, the postconditioning stress may either not have any effect at all when the low dose is too low, or may become harmful in case the low dose concentration is too high. For accurate assessment an experimental setting of postconditioning hormesis is required. The advantage of experimental systems is that a stress-induced diseased state can be manipulated by the dose of the inducing substance. When a diseased state is too mild, the organism recovers spontaneously at maximal speed. This offers no possibility for stimulation of recovery. When the diseased state is too severe, recovery is severely hampered. Even after application of diluted doses for curative purposes, a long experimental time may be necessary to observe stimulation of recovery. One can argue that an intermediate diseased state with highly significant clinical parameters is required to study effects. Examples of such parameters are mortality (for intact organisms) and cell viability (for in vitro cultured cells).

A MOLECULAR APPROACH TO POSTCONDITIONING HORMESIS

The present review focuses on a molecular biology research of postconditioning hormesis utilizing stressed "in vitro" cultured cells, in particular on the proteotoxic response of cells and the regulation of stress protein synthesis. Proteotoxicity, originally defined by Hightower [9] to indicate the detrimental action of denatured proteins in cells, is a phenomenon of increasing interest in biomedical disciplines. Damage to cellular proteins occurs following a variety of adverse conditions, such as: a.) after heat shock, b.) after ingestion of environmental pollutants such as heavy metals and c.) following ischemia. These changes in protein structure and consequently in their activity are considered primary symptoms. Denatured proteins are increasingly recognised as crucial factors in the development of various chronic diseases including neurodegenerative, atherosclerotic, diabetic, etc. and in the process of aging. [10-12] To limit proteotoxicity a set of hsp's (chaperones) are produced that are involved in cellular repair, recovery and defence mechanisms. Cells defend against misfolded ("toxic") protein aggregation utilizing two protein types: molecular chaperones (typically hsp27, hsp60, hsp70, hsp90 and hsp100) and the ATP-dependent proteases.[13] Initially, relatively simple experiments were used to test the hypothesis that stress proteins provide protection by increased cellular survival capacity. Upon comparison of the capacity to survive with the amount of stress proteins synthesized, a close temporal relationship was observed.[14] Other studies used variants of cell lines which constitutively have a higher level of survival capacity. These cells were analyzed for stress proteins and correlations were found with increased levels of hsp27, 60,70, 90 and 100.[15-17] Many studies have subsequently focused on how the presence of the stress proteins lead to an increase in cell survival capacity under threatening conditions. One of the concepts that emerged from the studies of stress proteins is their role in molecular chaperoning. As chaperones they have the capacity to bind to folding intermediates (misfolded or partly denatured proteins) and prevent their irreversible denaturation. It has since been demonstrated that chaperones possess many active functions: they repair structural damages by forcefully disentangle aggregated proteins, unfold and refold them into 're-educated and born again' functional proteins.[13, 18] The various stress proteins appear to be differentially induced depending on the stress condition.[19, 20] The question of relevance is now whether a postconditioning effect can be demonstrated at the molecular level of stress protein synthesis and changes in survival capacity. Within this framework, the homologous and heterologous postconditioning effect was studied on the stress protein response.

Homologous postconditioning hormesis

Homologous postconditioning studies were carried out with cells that were exposed to different initial stressor arsenite (100 or 300 μM), cadmium (10 or 30 μM) or heat shock (42ºC or 43.5 ºC). The data demonstrated that arsenite postconditioning treatment (1, 3 or 10 μM) increased survival capacity compared to cells that were

only pretreated with 100 or 300 μM arsenite.[21] The stimulation was dependent on the pre-exposure. A larger stimulation was observed when increasing low doses of 1, 3 and 10 μM followed pre-exposure of 100 μM arsenite. In contrast, cells pre-exposed to 300 μM arsenite only demonstrated an enhancement in the presence of 1 and 3 μM; 10 μM was detrimental. Similar data were obtained in homologous cadmium postconditioning hormesis studies. Data demonstrated that cadmium postconditioning ranging from 0.03 to 1 μM increased survival capacity in cells that were pre-exposed to 10 μM. When cells were pre-exposed to 30μM cadmium, survival capacity increased only when cultures were exposed postconditionally with 0.1 μM. Higher concentrations of cadmium (0.3, 0.6 or 1.0 μM) inhibited the development of survival capacity.[22] In the study on homologous heat postconditioning hormesis, cells were initially exposed at either 42°C or 43.5°C and 'postconditionally' incubated at mild (fever-like) temperatures (38-41°C). These mild postconditioning fever-like temperatures appeared to be beneficial following the 42°C heat treatment. However, the mild temperatures depressed survival capacity of cells exposed to 43.5°C.[23]

The effect of the three postconditioning treatments on the production of stress proteins was accordingly evaluated. When a treatment with 100 μM arsenite was followed by incubation under control conditions (arsenite-free medium), synthesis of the hsp60, 68, 70, 84, and 100 could be observed. When, however, the pretreatment was followed by homologous arsenite postconditioning incubation with low concentrations of arsenite, an enhancement of the synthesis of stress proteins was observed. The treatment with low dose arsenite alone (without pretreatment) did not cause any induction of stress proteins.[21] In homologous cadmium postconditioning hormesis, a transient increase in synthesis of stress proteins (hsp28, hsp32, hsp68, hsp70, hsp84, and hsp100) was demonstrated when cells were pretreated with 10 μM cadmium followed by incubation in a cadmium-free medium. When similarly pretreated cells were incubated in media containing a low (0.3 μM) dose of cadmium, an enhanced and prolonged induction of several stress proteins was observed.[22] Schamhart *et al.*[24] were the first to demonstrate a significant increase in the synthesis of specific stress proteins (hsp28, hsp60, hsp68, hsp70, hsp84 and hsp100) in homologous postconditioning hormesis with heat-shock and mild 'fever-like' temperatures. Similar observations were reported for mRNA levels of hsp68 and hsp84 when heat shocked cells were post-exposed to mild fever like temperatures.[23] These observations were further supported by the observation of Delpino *et al.*[25] who demonstrated an enhanced synthesis of stress proteins and an enhanced survival capacity due to this step-down heating protocol, in which a heat shock is followed by a mildly elevated (fever-like) temperature.

Heterologous postconditioning hormesis: Towards the Similia principle

With respect to the conceptual relationship between postconditioning hormesis and the homeopathic Similia principle, it is emphasized that the Similia principle is a particular application of postconditioning hormesis. The Similia principle implies that substances causing symptoms in healthy biological systems can be used to treat similar symptoms in diseased biological systems. The most straightforward application of this principle (also called "isopathy") is that a low dose of a specific substance may have a beneficial effect when applied following a higher dose of the same substance. However, the Similia principle includes more than Isopathy. In the homeopathic Similia principle, the main vehicles used to investigate this phenomenon are heterologous rather than homologous agents. Heterologous treatment includes a disturbance created with one substance and subsequently treated by *different* substances. Only when a range of different heterologous substances are tested for therapeutic effects, the Similia Principle can be studied. It is then possible to compare the effect of treatment with the degree of similarity between the diseased state and the effects caused by different substances. A more detailed elaboration on an example of a research program on the Similia principle at the cellular level, has recently been described by Wiegant and Van Wijk.[26]

In homeopathy, the selection of a remedy is based on the overall symptom pattern of the patient and includes subjective and objective symptoms. However, not all symp-

toms are equally important. The pattern of induced stress proteins (both heat shock proteins [hsps] and glucose-regulated proteins [grps]) is specific and was considered the sole indication to direct research as to the choice of the low dose agent to analyze the specificity of the similia principle.[27-29] The low dose conditions included arsenite, several heavy metal ions (cadmium, mercury, lead and copper), two different oxidative stress conditions (menadion and diethyldithiocarbamate) and a mild hyperthermic temperature. These stress conditions differ both in the extent as well as the pattern in which various stress proteins are stimulated.[20] The qualitative specificity, for instance, shows that lead (Pb) induces the grps (grp78/grp94), which are not induced by heat shock, other heavy metals or oxidative stressors. Only arsenite induces grp94 slightly. Heat shock and arsenite induce hsp60, whereas cadmium and ddtc do not.

Analogous to the symptoms that an agent is able to induce in healthy biological systems, the stressor-specific patterns of induced proteins can be considered 'remedy pictures' at the cellular level. The ability to quantify the 'overlap' between disease picture and remedy picture, a crucial prerequisite to study the similia principle, has then been met. Now this degree of similarity was established, the stage to study the specificity of low dose stimulation on cell survival capacity is reached. This was evaluated by analyzing the effect of a range of mild stress conditions that were used "postconditionally" following a heat shock.[29] This increase was labelled "survival stimulation factor". It represents the degree of stimulation of survival capacity as exerted by postconditioning with the positive control, the homologous stress. Heterologous postconditioning demonstrated an increase of the "survival stimulation factor". The increase appeared to depend on the nature of the small dose stressor. The stimulation of survival capacity correlated with the degree of similarity between the stress protein pattern induced by heat shock and the pattern of stress protein induction characteristic (specific) for the compounds that were applied in small doses.

To explain the variability of small dose stimulatory action on heat-shocked cells, it was hypothesized that such conditions only induce an increased survival if they are able to stimulate the specific endogenous defense and recuperative mechanisms that are usually activated in damaged cells. Since stress proteins are viewed as a reflection of the initiation of endogenous defense at the molecular level, the research evaluated whether observed differences in stimulation by small doses were related to the specificity in the overall pattern of stress proteins. Indeed a significant correlation was observed for most stress proteins between enhanced additional synthesis due to low dose stress and the degree of similarity between the inducing effect of individual hsps by high and low dose stress. It was also concluded that during the period of enhanced sensitivity, cells react to substances applied in low dose, to which they would normally not react, and that the stimulation of stress protein synthesis also depended on the similarity in effect between high dose and low dose stress condition (Wiegant et al.[29] for further details).

DISCUSSION AND CONCLUSION

Promising results indicating the beneficial effects of postexposure conditioning are emerging from basic research. This commentary paper presents a number of such additional reports from molecular biological research illustrating the therapeutic potential of postconditioning hormesis. In summary, the degree of stimulation by low doses of stressors that are applied post-conditionally appears to be stressor-specific. The specificity is not only present in the development of the survival capacity, but also in the subsequent enhancement of the stress-induced synthesis of stress proteins. The degree of stimulation of survival capacity by sequential low doses is determined by the degree of stress protein pattern similarity between the stress condition used as a low dose and initial high dose. This observation supports the validity of the similia principle at the cellular level. It is of interest that the beneficial effects related to proteotoxicity and stimulation of endogenous cytoprotective mechanisms also is dependent on the severity of the initial exposure condition. The more severe the initial stress conditions, the smaller the concentration required for stimulating stress protein induction.[21-23] These observations in the framework of homologous postconditioning are in agreement with the

"Law of Initial Values" formulated by Wilder [30, 31] According to this law, the higher the initial postconditioning stimulus, the smaller the response to a "function-raising" substance and the greater the response to "function-depressing" agents. Conversely, the lower the "initial level", the greater is the response to 'function-raising' agents and the lesser to function-depressing ones. It is suggested that the discovery of Hahnemann's *similia similibus curentur* ('let like be cured by like') is still worth-while in the twenty-first century. In this respect the comparative research on the relation between postconditioning hormesis and the homeopathic Similia principle is an interesting challenge for both science and homeopathy.

STATEMENT

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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EVALUATING HOMEOPATHIC DRUGS WITHIN A BIOMEDICAL FRAMEWORK

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ABSTRACT

The concept of hormesis can provide an evaluation framework for the assessment of homeopathic treatment preparations following a post-conditioning hormesis protocol based on the research of van Wijk and colleagues (Calabrese and Jonas, 2010; van Wijk and Wiegant, 2010). This proposal would require that doses of administered drug conform to analytical chemistry requirements for quantification. This developmental framework can provide a scientific "point of contact" between the homeopathic and biomedical communities which has long been lacking.

Key Words: Homeopathy, hormesis, hormetic, post-conditioning, biphasic, cAMP, wall lizard, phagocytosis, macrophage

INTRODUCTION

The present issue of the BELLE Newsletter/HET represents the first time in 20 years that it has addressed the issue of how hormesis and homeopathy may relate to each other (Calabrese, 2010A; Calabrese, 2001; Harrison, 2001). Reasons for this lack of formal external-open- literature evaluation are complex. The most important reason for the avoidance of such an obvious topic of historical relevance and current scientific debate has been the desire of many leaders of hormesis-oriented research not to allow the hormesis concept to be associated in any way with homeopathy (Calabrese, 2010B). Thus, there has been an intention to establish a "distance" between these two concepts, and thereby achieve an inference of distinction between hormesis and homeopathy with respect to their origins, scientific basis, capacity to be experimentally assessed and validated and applications. In general, those individuals who have developed and expanded the concept of hormesis over the past several decades have been educated and trained in traditional scientific methods, have long been part of the so-called scientific mainstream and have not been associated with homeopathy. Based on such an educational and experiential framework, homeopathy has been viewed as a medical practice, based on a philosophical perspective and not science. This perspective has been re-enforced by the administration of medicinal preparations in homeopathy practices in which presumed active ingredients were not likely to be present due to excessive and intentional homeopathically-based dilution practices (Calabrese, 2009). Although not "formally" considered, it was nonetheless clear from the start of BELLE that it would be essential to ensure that efforts to study and expand hormesis should steer clear of the homeopathic perspective. An association with homeopathy was seen as creating a severe detriment for a renewal of scientific interest in hormesis. It was thought that the linkage of the two ideas should be avoided at all costs. In fact, the historical association of the two concepts was viewed as a type of "scarlet letter" on the "face" of hormesis (Calabrese, 2001). It was this association that had to be weakened, if not broken. Hormesis was seen as legitimate, mainstream science, being testable, vali-

dated, reproducible, evolutionarily founded and mechanistically based. In contrast, homeopathy is a medical practice that seemed to reside in a fuzzy state that encompassed philosophical and, indeed, spiritual concepts, all mixed within a curious but unconvincing blend of technical and scientific activities, some of which were simply perplexing, especially to those in the scientific and medical communities outside of the homeopathic world. Since professionals are very intent on protecting their reputations it was clear that no one associated with BELLE wanted it to be perceived as part of, or sympathetic to, the homeopathic perspective. At the same time it was somewhat frustrating to observe a seemingly steady stream of homeopathic-oriented publications that linked homeopathy with hormesis (Clement, 1997; Eskinazi, 1999; Satti, 2005; Mastrangelo, 2007), possibly trying to take advantage of its (i.e. hormesis) growing success within the scientific literature and broader scientific community. Despite such efforts by some in homeopathy and concerns by leaders in the BELLE/hormesis domain that such activities/publications could adversely affect the expansion and acceptance of hormesis within the scientific community, hormesis has made phenomenal progress over the past 15 years in establishing its distinctness from homeopathy, its credentials in mainstream science and has now earned its place in leading textbooks of toxicology (Klaassen and Watkins, 2003; Hayes, 2008), pharmacology (Hacker et al., 2009), and the broader biomedical sciences (Le Bourg and Rattan, 2008; Mattson and Calabrese, 2010; Sanders, 2010). This progress is also reflected in the broad range of scientific disciplines in which hormesis has displayed striking increases in literature citations. For example, in the entire decade of the 1980s the terms hormesis or hormetic were cited about 15 times per year in the Web of Science database. In 2009 alone they were cited nearly 2500 times, greater than a 150-fold increase (Figure 1).

Despite this desire and need to distinguish itself from homeopathy, this situation became dramatically changed because of three unrelated, yet intersecting activities. First, in 2007 nearly 60 high level biomedical scientists proposed a new and integrative biological stress terminology based on the hormesis framework (Calabrese et al., 2007). Of relevance was that this terminology integrated the profoundly important concepts of pre- and post-conditioning, demonstrating that they are manifestations of hormesis (Calabrese, 2008). Second, we subsequently re-evaluated the research by van Wijk and colleagues, who had developed an experimental therapeutic model system as a means to study possible homeopathic effects. Their methodology showed considerable promise, providing reproducible experimental findings of low dose enhancement of adaptive responses subsequent to an exposure to chemical/physical stresses employed to simulate a human disease condition. Despite their potential value, these findings failed to gain traction within the biomedical community. Of interest to the hormesis concept was that the methodology of van Wijk and Wiegant (2010) was fully consistent with the Calabrese et al. (2007) experimental features in which post-conditioning hormesis would be assessed. This intersection of homeopathy and hormesis is "point of contact" – to use a term of Bellavite et al. (2010) – and was worth exploring as a start and perhaps there might be other so-called points of contact once this interrelationship could be more dispassionately considered. Third, since considerable progress had been made for hormesis in securing a strong scientific foundation and its broad acceptance within the scientific community we felt sufficiently confident that hormesis could facilitate the testing of homeopathy via modern biomedical methods without adversely affecting its widely improving reputation. The issue of dose/exposure is key to establishing a point of contact between hormesis and homeopathy and it is why the post-conditioning esperimental model of van Wijk and Wiegant (2010) can be a vehicle to start a constructive scientific dialogue between homeopathy and the modern biomedical sciences. This framework, as noted above, works in the traditional realm of quantifiable dose to target organs or cells. It puts different hypotheses on a similar footing, all within a post-conditioning, standard therapeutic operational framework.

It was within this framework that the present collection of papers was invited. We sought a broad range of perspectives, including those from homeopathic theoreticians (Fisher, 2010), researchers (Belelvite et al., 2010;

van Wijk and Wiegant, 2010; Oberbaum et al., 2010), and practitioners (Bernardini, 2010; Fisher, 2010) as well as strongly opposing skeptics (Moffett, 2010) and more open-minded skeptics (Rattan and Deva, 2010) and invited all to wrestle with the general question of how hormesis and homeopathy might be related, using our initial proposal of the post-conditioning hormesis framework as a focus for discussion, but not letting it restrict their thinking. A reading of these papers reveals how such leaders view hormesis, its potential applications to the field of homeopathy, and how hormesis may provide a vehicle to test homeopathic remedies within a biomedical domain. These papers speak for themselves and illustrate how this topic can be constructively addressed and engaged.

We would like to finish this summary by proposing a second possible "point of contact", that of finding opportunities to assess hormetic responses at very low concentration which have biomedical applications. This type of example maybe of considerable interest to the homeopathic community given the low dose concept and thus create that second point of contact. Hormetic responses have been typically studied in vitro at concentrations ranging from about 10^{-12} to 10^{-6} M, a profound distance from that often seen in the publications of high dilutionist homeopathy. In such cases a concentration of 10^{-30} M may be commonly employed while any concentration less than 10^{-23} M (Avogadro's number) might not have any molecules present. Thus, there is no apparent point of contact between hormesis and homeopathy in the below Avogadro's number zone. We realize that investigators have learned much about the physical chemistry of water as a result of studying ultra-high dilutions used in homeopathy (see the paper of Fisher, 2010). Perhaps these studies will yield important new findings that will generate a new point of contact between homeopathy and pharmacology/toxicology. We do not believe this is the case at present. However, there are numerous examples of hormesis at concentrations below 10^{-12} M with a broad range of biological models, endpoints and chemicals. One such example was noted by Roy and Rai (2004) concerning the effects of catecholamines on macrophage phagocystic capacity of the wall lizard. In their study they reported that cAMP, acting as a second messenger, enhanced this stimulatory/adaptive response at a concentration (10^{-18} M) that yielded about 120 molecules per 400,000 cells (i.e. one cAMP molecule per 3333 cells). Figure 2 provides a representation of this striking concentration response relationship. The low concentration of cAMP stimulated new protein synthesis that then lead to enhanced phagocytosis in macrophages, thereby indicating a genomic pathway in the low dose stimulatory response. Blocking of this process by transcription and translation inhibitors prevented the low dose stimulation. However, these inhibitors did not affect the high dose inhibition, suggesting a non-genomic pathway for the high dose inhibitory effect. Based on Figure 2, the response would likely occur at even lower concentrations, that is, fewer molecules per cell. While the mechanism of this response needs further elucidation it suggests a wide range of possibilities including that of inter-cellular amplification via a cell to cell communication mechanism. The recognition that critical messages can be sent via the use of a relatively small number of molecules indicates how highly effective biological communication processes can be. This type of experimental model may also hold promise as another point of contact between hormesis and homeopathy. We think that a model system that uses very low concentrations of messenger as in the case of the wall lizard immune function may provide an example which could be jointly explored between the homeopathy and biomedical communities.

Finally, we appreciate the comments of Fisher, 2010 that our "white paper" (Calabrese and Jonas, 2010) generated more light than heat. We are also hoping that our summarizing comments have also done so by clarifying past actions of BELLE as well as in the proposed model system which would permit the assessment of homeopathic and allopathic drugs within a post-conditioning hormesis experimental framework. We would encourage and challenge the biomedical and homeopathic communities to offer their own insights on how to explore these disciplinary intersections via new articles and letters to the editor.

Figure 1. Citations of hormesis/hormetic in Web of Science Database

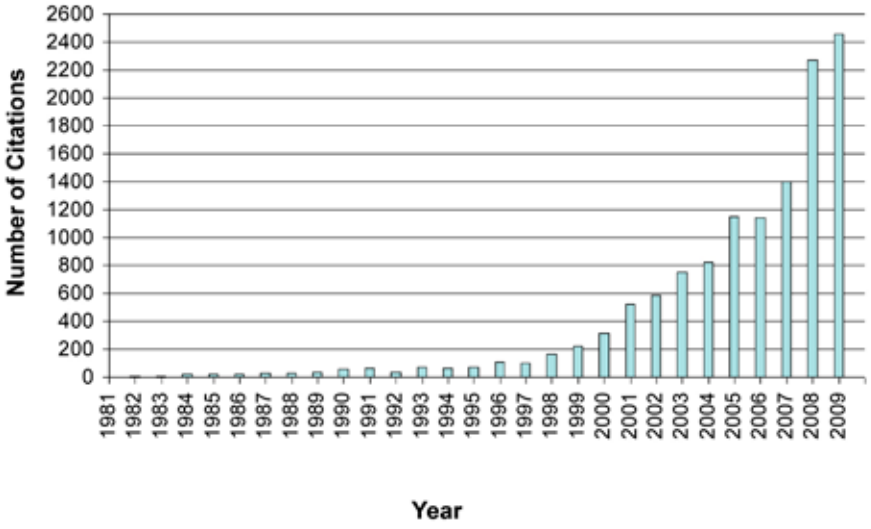
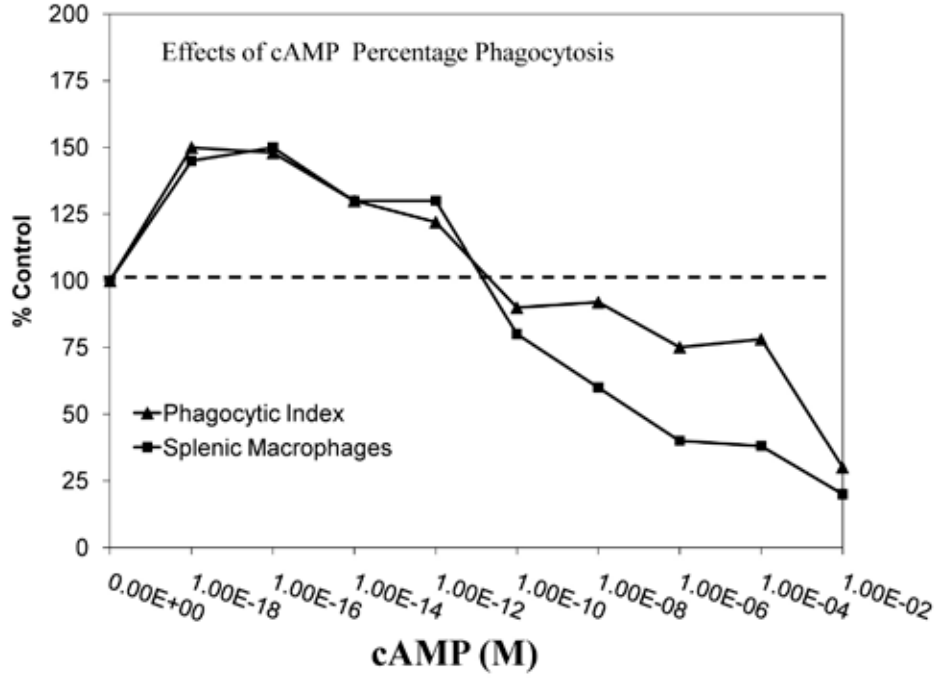


Figure 2. Effects of cAMP on percentage phagocytosis (source: Roy and Rai, 2004)



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