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Letter to the Editor

Dose-Response:
An International Journal
October-December 2017:1-4
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DOI: 10.1177/1559325817744451
journals.sagepub.com/home/dos
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Hormesis and Homeopathy: Toward a New Self-Consciousness

Andrea Dei[1]

Contrary to common belief, most new discoveries and theories are not merely additions to the existing stockpile of scientific knowledge; in order to assimilate them, the scientist usually has to rearrange his intellectual mind, discarding elements of his own previous theories. In this sense, he plays the role of a divergent thinker since the scientific community is often not ready to accept a new position for many reasons, among which not only lack of flexibility and open-mindedness but also political and economic interests. The gist of this thought[1] by Thomas Kuhn can be found in an important editorial by Edward Calabrese which recently appeared in *Homeopathy*.[2] The editorial concerns a manuscript published by Bellare and coworkers in the same issue of the journal,[3] in which the authors show that nanoparticles of different metals, that in previous articles had been unequivocally found at concentrations of a certain pg/mL in 30 CH and 200 CH homeopathic remedies,[4,5] induced a biological response. Furthermore, the authors reveal that the biological responses induced by these homeopathic remedies show the traits that would normally characterize a hormetic dose–response mechanism.[6-11] Taking into account that both homeopathy and hormesis, as well as their mutual relationships, are attractors of criticism and controversy,[12-19] this result, in Calabrese's opinion, is extremely significant. Using Calabrese's words, it shows once again what happens when some scientists actually try to understand the physical system and what happens within it, while others are simply dismissive. In this context, there are a few more points I want to mention here that deserve particular consideration.

Two important sets of experiments have been reported in the last few years. The first concerns the above-mentioned studies by the Bellare group using electron diffraction and electron transmission microscopy techniques.[4,5] These studies show that, contrary to any previous beliefs, when homeopathic medicines containing metal nanoparticles are progressively diluted and succussed, highly diluted solutions contain an unexpected amount of the original substance. According to the authors, this is due to the formation of an enriched monolayer of nanoparticles on the surface due to froth flotation induced by succussion, that is, a particular vigorous shaking procedure. This monolayer is maintained in the dilution process. Two points are worth mentioning here: firstly the highly diluted solutions contain a roughly 6 CH asymptotic concentration which does not depend on the serial dilution, the observed amount of nanoparticles being consistent with those usually observed in monolayers of absorbed materials on solid surfaces (10^{12}-10^{14} molecules/cm^2).[20,21] In addition, the authors point out the active role of hydrogen metasilicate oligomers, whose donor properties contribute to the stabilization of the monolayer constituent units themselves. The succussion procedure itself means that all the diluted and succussed solutions contain metasilicate oligomers due to the glass containers.[22] Their relevance in homeopathy has already been stressed.[23]

The second set of experiments concerns DNA microarray studies, that is, a technique which provides an important tool to understand the very heart of the biological network system through the measurement of gene expression profiles. Studies reported by several research groups show that homeopathic medicines of different concentrations affect the gene expression profiles of different DNA microarrays when compared with controls.[24-32] This effect is significant even for very diluted solutions (i.e. 15 CH or 30 CH, which roughly correspond to 10^{-30} and 10^{-60} M), involving the presence of a number of molecules well beyond Avogadro's number. In other words, the action of drugs is not suppressed by ultrahigh dilution and proceeds through the modulation of gene expression, thus indicating that their efficacy is maintained. This result would seem to have 2 consequences: (1) the *tenet* that any drug must contain particles which interact in a specific way with the

[1] Department of Chemistry, INSTM Research Unit, University of Florence, Florence, Italy

Received 04 October 2017; accepted 17 October 2017

Corresponding Author:
Andrea Dei, Department of Chemistry, INSTM Research Unit, University of Florence, Via della Lastruccia 3, 50019 Sesto F.no, Florence, Italy.
Email: andrea.dei@unifi.it

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biological substrate does not hold and (2) solutions may infer a type of information which challenges the quantization of matter dogma. These results would therefore support the efficacy of homeopathy due to certain mysterious mechanisms. Hypotheses like water memory,[33-35] quantum mechanical effects like bio-phonons and resonance coherent domains,[36-39] or clathrate formation[40] have been proposed and obviously strongly criticized by the scientific community.[41] To date, the statement that homeopathy constitutes a holistic approach (which as a healing system goes far beyond any specific information) appears the most appropriate in its vagueness and scientific uncertainty. However, it is important to stress another important point which could be considered crucial to clarifying the problem: All the above-mentioned research used a single dilution of the homeopathic preparation. Studies carried out by 2 independent groups[42-47] show that by treating the DNA microarrays with homeopathic remedies (*Gelsemium sempervirens* and *Apis mellifica*) in different concentrations, including 15 CH and 30 CH, the response of the biological system decreases with increased dilution of the homeopathic medicine. In addition, the observed patterns of gene expression profiles are consistent with hormetic mechanisms; in other words, they are characterized by the same common denominator as the concentration-dependent inversion of the gene expression, as has been seen to occur not less than 3 times in a human prostate epithelial cell line treated with copper(II) solutions, with concentrations ranging from 10^{-6} to 10^{-17} M.[48] These results are also supported by polymerase chain reaction (PCR) experiments.

It is hard to understand and to accept that the water memory (and the others of the above-mentioned physical proposals) should be affected by serial dilution. Therefore, it seems reasonable to suggest that the latter results are consistent with a drug concentration which is different from that expected. The conclusion is different from the Bellare group,[3-5] which suggests a constant number of metal nanoparticles below a certain metal concentration, despite the serial dilution. However, both sets of experimental results support the very important suggestion that homeopathic solutions can be defined as "nonsolutions," their classically postulated homogeneities being eliminated by the presence of larger populations of "solute" molecules at the liquid–vapor interface rather than in the bulk. For *Gelsemium sempervirens* and *Apis mellifica*, this may occur, for example, if hydrophobic interactions are operative and/or the molecules exhibit self-association in water, a quite common feature of the majority of organic drugs. The formation of molecular nano-associates in aqueous solutions, which were prepared using serial dilution, has recently been reported and discussed.[49] This may justify the formation of a surface layer; in this case, the number of molecules at the interface decreases smoothly with dilution, whereas the number of solute molecules in the bulk follows the expected linear decrease with dilution. Since homeopathic remedies are prepared by diluting and succussing a concentrated solution, it can be expected that the number of molecules which populate the interface is small compared to those in the bulk. Therefore, in practice, we observe first the canonical linear dilution behavior and then a less enhanced dilution effect due to the preferential solute–solute interactions at the interface. It is obvious that the peculiar nature of the layer depends on the details of the species, and this may explain the difference between metal nanoparticles and organic molecules. In addition, for *Gelsemium sempervirens* and *Apis mellifica*, this fact may play a role since the natural remedy is made up of many different components. However, if the above arguments hold, it can be argued that the majority of homeopathic remedies are always at nonzero concentration, against any formal expectation. This is difficult to demonstrate using the same physical techniques employed by the Bellare group, due to the different nature of the substances investigated (metal nanoparticles vs organic molecules), but it seems to offer a rationale to the observed pattern of reactivity toward DNA microarrays.

Both sets of experiments are therefore consistent with the here-defined "nonsolution" character of homeopathic medicines and support the hypothesis that in their interaction with the biological substrate hormetic mechanisms are operative. If this statement holds, homeopathy should not be considered a nebulous therapeutic approach, where, as is believed and claimed at present, unclear mechanisms of information transfer operate to shift a living organism from a pathological attractor toward a normal physiological one. Homeopathy is simply reduced to a microdose pharmacology where drug molecules "traditionally" interact with a biological system, which in agreement with the principles of nonequilibrium thermodynamics, Lamarckian evolution, and its own autopoietic nature, exhibits a dose–response hormesis response which justifies the *simile* therapeutic philosophy.

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