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Review Article

Towards a Rational Insight into the Paradox of Homeopathy

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Abstract

Biological efficacy of infinitesimally diluted substances is still controversial. However, homeopathic remedies are manufactured through an iterative dilution/dynamization procedure which induces collateral phenomena, especially nanobubbles and release of silica from the glass container. Our own NMR studies and a review of the literature show that dilutions could contain much more molecules than expected, moreover in nanoparticulate forms which increase with dilution. Dilution/dynamization beyond a threshold of 10^{-6}-10^{-8} generates superstructures associated with the solute, which grow at each step by affixing layers of nanobubbles and silica, or by self-assembly. Sizes from 1-2nm to hundreds of nanometers could be demonstrated by electron microscopy. Dynamization appears crucial, by producing specific superstructures (distinguishable according to the dissolved substance), and inducing paradoxical biological effects. Superstructures are neither observed without dynamization nor at low dilution, where even a paradoxical chaotropic effect on the solvent is observed by NMR. Thus, a dual structure of the homeopathic medicine is highlighted. We postulate that dynamization and nanobubbles ensure formation, stereospecificity, growth and transfer of superstructures across dilutions. The sampling tip may play a major role by catching the superstructures and conveying the encaged remedy across the successive dilutions. Some studies managed to show the presence of the remedy source, as a non-zero asymptote, in ultrahigh dilutions, far beyond the Avogadro's limit. Owing to this physical duality, low dilutions would act on organ receptors through ligand-receptor interactions, and high dilutions on systemic size-dependent targets, due to peculiar properties of nanoparticles, able, as a function of size, to cross physiological barriers, stimulate endocrine and immune systems or enter nerves to directly reach the brain. Inverse effects, observed within the 10^{-3}-10^{-6} range, might correspond to the onset of the nanoparticulate form. The number of dynamizations could be the true factor for biological activity, rather than the rate of dilution.

Keywords: Homeopathy; Ultrahigh dilutions; NMR relaxation; Dynamization; Nanobubbles; Nanostructures; Homeopathic remedy as nanomedicine; Hormesis; Hypotheses about biological effects

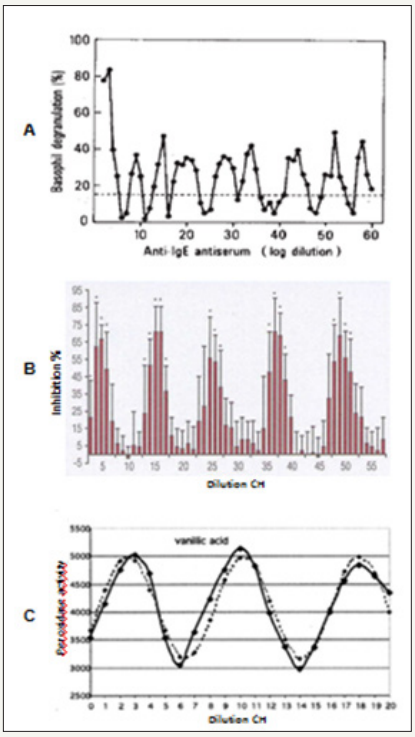
Abbreviations: NMR: Nuclear Magnetic Resonance; NS: Nanostructure; NB(s): Nanobubble(s); NP(s): Nanoparticle(s); DLS: Dynamic Light Scattering; R/B: Rayleigh/Brillouin; (T)EM: (Transmission) Electron Microscopy; AFM: Atomic Force Microscopy; BBB: Blood-Brain-Barrier; OB: Olfactory Bulb

Introduction

Today, despite non-recognition and even opposition by scientific and medical institutions, homeopathy is the most widely used form of alternative medicine in the world. According to the World Health Organization, approximately 500 million people worldwide are treated by homeopathy. It is also used widely by veterinarians. Its origin goes back to Hahnemann [1] over 200 years ago. It is based on the "law of similia": a substance that elicits symptoms in a healthy organism is able to cure similar symptoms in a diseased organism. Despite positive meta-analyses of hundreds of studies-clinical [2-6], biological [7,8] and physicochemical [9]-its efficacy remains a subject of controversy due to trials judged to be insufficiently reliable [10-14]. Yet a recent review established the good quality of the physicochemical research in this field [15]. But the main reason for mistrusting homeopathy is ignorance concerning its mode of action, especially incredulity towards the action of infinitesimally diluted substances. In accordance with the pharmacopoeia, homeopathic remedies are prepared following a specific iterative centesimal dilution/agitation procedure-also called dilution/dynamization, dilution/succussion or potency-(with C1 corresponding to a 10^2-fold dilution, and Cn to a 10^{2n}-fold dilution), so that the initial solute is virtually no longer present beyond C12 (Avogadro=$6x10^{23}$).

Yet ultramolecular dilutions, such as C15 and C30, are regularly prescribed in France and much more highly diluted solutions (C100, C200,...) are prescribed in other parts of the world. The stumbling block is here: a theoretical implausibility that legitimately leads to its being considered a placebo. Moreover, the target of the remedy differs according to the level of the dilution.

C3-C5, so called low dilutions, are effective for organic or limited functional disorders (localized inflammation, digestive disorders, ENT infectious disease,...), whereas higher C7-C9 and C15-C30 dilutions are effective for general symptoms (fever, asthenia, hypertension, nerve pain) and psychic symptoms. The action of low dilutions is short and must be repeated, whereas the action of high dilutions is more durable and sometimes highly durable. Too, homeopathic remedies have the particularity of a periodic efficacy, well described in biology, which is sometimes virtually sinusoidal, as a function of dilution (Figure 1); [16-18]. Because all of these characteristics differ so radically from rational pharmacological schemas and the laws of physicochemistry, scientific and medical communities have legitimately come to the conclusion of a placebo effect, systematic bias or non-reliable studies. This article is based on over 25 years of our own research in physics [19]. We endeavor to integrate recent data and hypotheses from the literature into a coherent model of the nature of homeopathic remedies and their mode of action that will address the questions cited above and by doing so provide a less irrational view and provoke a more serene debate on homeopathy.



Figures 1 : Biological activity of centesimal high dilutions.

A. Human basophil degranulation by dilutions of anti-IgE antiserum (dynamized by vortexing). Reproduced from Davenas et al. [16] with permission.

B. Inhibition of human basophil degranulation by dilutions of histamine (dynamized by vortexing). Reproduced from Sainte et al. [17] with permission.

C. Horseradish peroxydase activity measured in the presence of diluted vanillic acid (dynamized by succussions). Reproduced from Malarczyk et al. [18].

Part 1: On the Physical Nature of Homeopathic Remedies

Non-plausibility of the "Memory of water"

The theoretical absence of residual molecules of active ingredients in ultramolecular dilutions has led to the development of several theories to explain the transfer and storage of information from the initial ingredient to the water of the solvent: imprint theory [20], clathrates [21], electromagnetic transfer [22], water coherent domains (quantum field theory) [23-25]. The hypotheses of electromagnetic transfer by the team of Benveniste et al. [22] (the "Memory of water" controversy), was recently taken up by Montagnier et al. [26,27] and discussed in the framework of the quantum field theory. The literature on these subjects is extremely abundant (review in [28]). It concludes that these are speculative models and at present there is no convincing evidence for a non molecular transfer of bio-information to the solvent. The pioneering experiments of Benveniste's team could not be reproduced [29]. The experiments of Montagnier et al. [30] showing that DNA sequences can be reproduced from an electromagnetic signal raise the fundamental question of how water can store and receive electromagnetic information with such precision that a DNA sequence can be reproduced without a template; such extraordinary promising results need to be confirmed by other teams and to prove that there was no contamination. According to the quantum field theory, the electromagnetic signal emitted by a molecule of solute would be "trapped" and stored in coherent water domains of approximately 100nm containing 5.5 million water molecules. However, structures such as these have never yet been demonstrated in pure water nor in ultramolecular solutions, i.e. in proved absence of any impurity, contaminant or remnant of solute. Up until now, the longest life of any structure observed in pure water has been of the order of 10^{-12}s [31].

High dilutions, even ultramolecular, are not pure water

Pure water does not exist, because even the most purified solution after distillation and ultrafiltration will contain dissolved gas and traces of contaminants, coming from the atmosphere and the walls of the containers. Moreover, the specific iterative method of preparation consisting in a dilution by pipetting and vigorous agitation-a process without which there is no biological activity-must imperatively be taken into account. Preparations are done in laboratory conditions, generally with equipment made of glass, but sometimes in polyethylene. The dissolution of air and the release of various chemical elements by the container are exacerbated by the dynamization process [32]. Recently, Si, Na and Ca have been clearly identified, at nearly the same amounts, in C30 dilutions of copper and in pure water controls prepared in glass containers in the strictly same conditions [33,34]. The authors concluded that homeopathic solutions cannot be considered as pure water as commonly assumed. We will focus on the two major factors induced by the dynamization process, i.e. silica and nanobubbles (NBs).

Silica

Silicon dioxide SiO_2 (silica) is the principal ingredient in glass which dissolves in water to form silicic acid $Si(OH)_4$. High levels

of silicon, with higher than expected amounts in ultramolecular (C12-C21) dilutions of silica/lactose, were reported for the first time by Demangeat et al. [35,36]. High levels of silicon in various kinds of ultramolecular dilutions, even at C30, were confirmed later by other teams [33,37,38]. As the solubility of SiO_2 and $Si(OH)_4$ is very limited, the progressive enrichment of the solution through the dynamization process, leads to the formation of polysilicates and colloidal particles. Noteworthy, the presence of silicon, in the form of colloidal or micro-porous silicate, could be directly demonstrated in homeopathic dilutions by electron microscopy (EM) [37-39]. The potential role of silica has led to two interesting hypotheses on the mechanism of information transfer in the context of "Memory of water". According to the "silica hypothesis" [40], the silicates polymerize into remedy-specific patterns by catalytic action of the remedy source; for dilutions above C12, i.e. theoretically without molecules of remedy left, structured silicates act as the catalysts or templates for perpetuation of the remedy-specific patterns. According to "epitaxy" [41], transmission of structural information is carried out from the surface of a solid material to a liquid; silica nanostructures formed during dilution/dynamization may acquire and convey information from the remedy source material into the high dilutions.

Nanobubbles

The presence of air NBs in high dilutions, as first suggested by Roy et al. [41], was indirectly shown using NMR [36,42] and Rayleigh/Brillouin (R/B) scattering [43], and then directly confirmed by high-speed videography [44]. Outside the field of homeopathy, NBs had already been suggested in low concentrations of small organic molecules by Dynamic Light Scattering (DLS) [45]. NBs result from increase of gas dissolution, and/or cavitation, during the dynamization step, carried out either by strong vertical hand succussions, mechanical vertical stroking, vortexing or sonication; they are tiny bubbles, nanometer-sized, demonstrated by small-angle neutron scattering [46]. They do not rise in liquids, contrary to micro- or larger bubbles, and their amazing properties are longevity (days, months) (review in [47]). They have a strong propensity to coalesce and self-organize and have a strong affinity for hydrophobic surfaces; adsorption of ions or hydrophobic molecules on their surface increases their stability.

Evidence for nanostructures in high dilutions

Nanosized supramolecular structures (nanostructures, NS) in high dilutions, especially in the ultramolecular range, that do not exist in similarly treated controls, have been demonstrated by NMR relaxation by Tiezzi [48] and Demangeat [19]. The conclusions were based on the increase in the T1/T2 ratio, a parameter which reflects a reduced dynamics of water molecules, when constrained in a higher degree of organization, compared to pure water. The minimal size of the domain of constrained water molecules was calculated at about 4.2nm in diameter by Demangeat [42], a value recently confirmed at 3.7nm by a different team with the same technique [49]. Demangeat [36,42,47] showed that the size of the NS was growing with increasing dilution, and estimated it up to 80nm from the results of Tiezzi [48]. Using various physical techniques [50,51], Konovalov also observed unexpected 100 to 300nm-sized molecular assemblies, called nanoassociates, in ultramolecular dilutions of various substances, from simple molecules to complex microcyclic compounds. These nanoassociates were not observed in the absence of a solute. The smallest ones were 80nm-sized, and the size generally increased with dilution; moreover, depending on the nature of the substance, sizes could exhibit one or several maxima at high dilution levels. Montagnier et al. [26] also showed 20 to 100nm superstructures in dilutions of DNA sequences. Outside the field of homeopathic dilutions, large long-lived supramolecular structures of water [52,53], involving rather stable NBs [45], have been shown using laser-light scattering around low molecular mass compounds.

Arguments for the involvement of NBs in the nanostructures

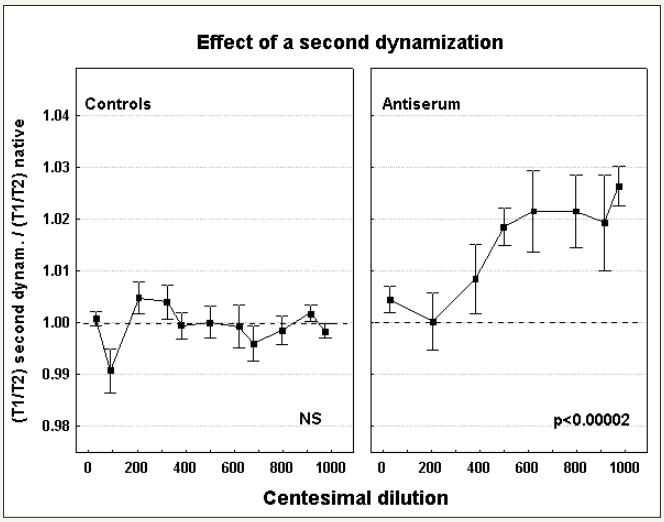


Figure 2: Effect of a second dynamization on T1/T2 in dilutions of antiserum and in controls [47]. The increase in the T1/T2 ratio reflects the enhancement or the regeneration of nanostructures in dilutions of antiserum that were left a few months after their preparation. Sizes clearly increase with increasing dilution. No effect was observed in controls.

The first evidence was brought with dilutions of histamine [42], and confirmed with dilutions of silica/lactose [36], owing to the total vanishing of all the NMR signals which characterize NS after a short heating/cooling cycle. Implication of NBs in the formation of NS could also be demonstrated with dilutions of immunoglobulins: NS were enhanced and/or regenerated by a second dynamization a few months after the initial preparation, in comparison to control samples (Figure 2); [47]. Montagnier et al. [26] noted that dynamization (which generates NBs, as we emphasize) was essential in the production of NS, and that these were destroyed by heating. Duval et al. [43] using R/B scattering, demonstrated long-lived sub-microscopic bubbles in dynamized high dilutions of NaCl and LiCl in water, and showed that a second shaking a few days after the preparation resulted in a marked enhancement or even an emergence of the R/B scattering. Jin et al. [45] using DLS, identified NBs as the origin of the supramolecular structures in dilutions of small organic molecules. These authors could remove the DLS signal characterizing the superstructures by filtration, and regenerate it by injection of air. All of these findings emphasize the crucial role of dynamization, and especially seem to corroborate the observations of Hahnemann and of some homeopaths that prefer that patients self-administer remedies in water after additional succussions.

Non evidence of nanostructures at low dilution

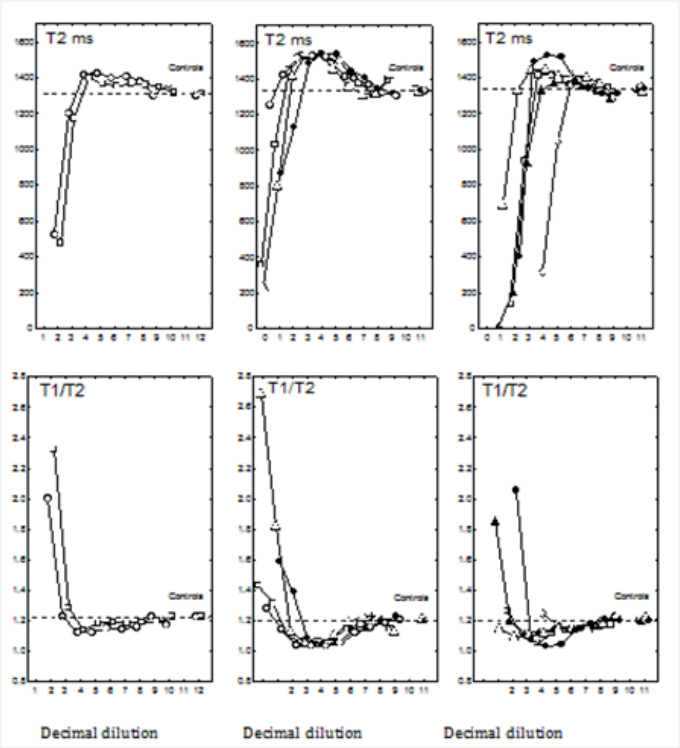


Figure 3: Paradoxical behavior at low decimal dilution [19]. According to the theory, the ratio T1/T2 reflects a reduced motion and/or a structured state of water molecules in solutions. The nadir in T1/T2, observed here within the D3-D5 (10^{-3}-10^{-5}) range in average, lies beneath the values of the controls. Such a behavior reflects a less ordered structure of water in the dilutions than in the aqueous solvent, what is called a "chaotropic effect" (it is worth recalling that bulk water at ordinary temperature exists in a highly ordered hydrogen-bonded tetrahedral structure). Beyond the nadir, the re-increase in T1/T2 upon further dilution corresponds to the formation of growing superstructures. The nadir indicates the transition between a highly ordered state of water within the hydration shell of the solutes at high concentration, and a highly ordered state of water within superstructures at higher dilution.

NMR experiments revealed a paradoxical behavior at low dilution (Figure 3) [19]. In the first decimal dilutions of several substances, a paradoxical chaotropic effect was observed, reflecting a transient destructured state of the solvent. Nanostructures only appeared beyond a dilution rate of 10^{-5}-10^{-7} on an average, attributed to a threshold of the air/solute ratio, needed to nucleate and stabilize the solute-NBs complex [19,54]. Montagnier et al. [26] too, did not observe NS below the 10^{-5}-10^{-12} dilution range. Konovalov et al. [51] using atomic force microscopy (AFM), reported a bimodal pattern of superstructures. Nanoassociates of hundreds of nanometers in size were only observed at high dilution, whereas the structures observed below 10^{-6}-10^{-8} merely consisted of aggregates (this corroborates Samal & Geckeler's [55] unexpected report of aggregation of fullerene conjugates in water whose size increased steadily with dilution). The dilution range between 10-5 and 10-8 seems to represent a key-threshold in the fields of physicochemistry and biology. Indeed, many papers reported more or less sharp physicochemical transition phases in dilute electrolytes [43,56-58] and non-electrolytes [55,59]; and quantum electrodynamics predicts a sharp evolution towards macro-coherent domains in dilutions of ions or non-electrolytes solutes beyond a critical dilution [25,60,61]. Strikingly, this rate of dilution corresponds to the threshold for the hormetic dose-response reversal observed in pharmacology and toxicology (Figure 4) [62].

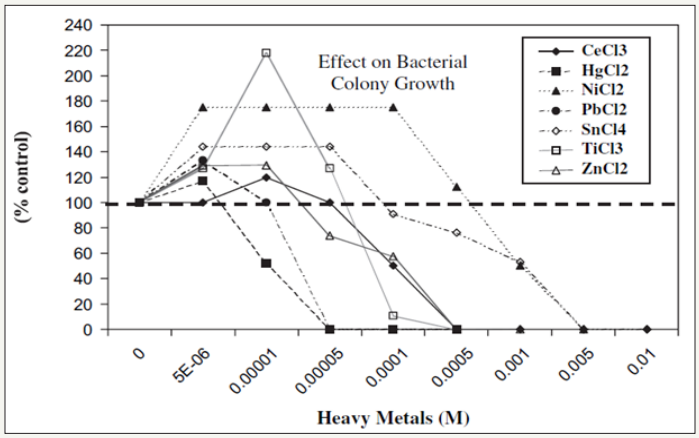


Figure 4: Typical hormetic dose-responses (from [62]) showing the reversal of effect (toxic at high concentration/stimulatory at low concentration). The transition occurs within the 10-3 - 10-6 M range. Note the striking similarity (except inverse abscissas) with the T2 variations of the same heavy metal chlorides investigated in Figure 3 (middle and right).

Size-activity relationship of nanostructures

Variable and even paradoxical clinical and biological activity with the rate of dilution of a substance, has been widely described in the literature of homeopathy (with periodic fluctuations (Figure 1)), pharmacology and toxicology [62-68]. These behaviors are not elucidated but have given rise to different types of appealing hypotheses [65-67]. Especially, Bell et al. [65,66] proposed a model for homeopathic remedy effects based on the hypothesis that the source remedy is present in homeopathic dilutions in the form of nanoparticles (NPs) by association with the silica coming from the glass (this point will be amply discussed below). Indeed, biodisponibility and bioreactivity are strongly dependent on size, shape and charge surface of NPs. Several authors have clearly demonstrated the crucial influence of the size of NPs on their biological activity [69-75]. Notably, some drugs possess pharmacological activity at ultra-low doses only in the form of NPs with a diameter of 100-300nm [72] and Konovalov et al. [51] could show that maxima in the sizes of nanoassociates did indeed correspond to maxima in bio-effects.

Nature of the nanostructures

The superstructures observed in high dilutions are essentially composed of the remedy source, of NBs, of highly structured ice-like water around NBs (clathrates), and of silica released from the glass [19,36,42]. They may contain lactose if any, when the preparation includes initial steps of trituration (this is the case for insoluble sources such as metals). Furthermore, they are boosted and probably stabilized by the presence of ions in the solvent [19], or by ions released by the glass. The presence of the remedy source is an essential condition for their formation, as they are not observed in controls prepared in the same conditions [19,50,51]. However, their structure is not elucidated. AFM images [51] showed nanosized particles mainly composed of water with enhanced viscosity, related to their constrained motion, which corroborates the NMR relaxation findings. So, nanostructures may result from a "nucleation process", or "seeding process", induced by the solute (and lactose if any), possibly catalyzed and stabilized by silica as an internal frame and/or coating layer. It would be misleading to give a univocal model of this nucleation process, insomuch as it must depend on the nature of the source remedy (molecular complexity for plant and animal extracts), the respective sizes between solutes and NBs, and the amount of silica. It is worth pointing out that dilutions/dynamizations of lactose itself, prepared as controls, also generate NPs [33].

Mechanism of transfer of the remedy source across dilutions

It has been postulated by Demangeat [47,54] that the NS are more or less rigid edifices which protect the "trapped" solute against out-diffusion, and behave as nucleation (seeding) centres for the subsequent dilutions. At each dilution step, the NS grow either by successive coating with NBs, ions and silicates, of by self-assembly. The sampling pipette or tip used in the preparation plays an active role by catching the NS and thus convey the encaged solute across the iterative dilutions, possibly up and beyond the Avogadro's limit. Indeed, glass pipettes are surrounded by an electric field; and plastic tips, which are hydrophobic, have a strong affinity for NBs. This would lead a pick-up of NS through either electrostatic or hydrophobic attraction mechanisms. Chikramane et al. [44] analyzed the process of dilution/dynamization of some metal powders using high-speed videography and proposed a rather similar mechanism involving NBs, based on froth flotation. They hypothesized that NBs "frost" the NPs of the source material, allowing them to rise in the liquid through attachment to larger bubbles and be picked-up by the sampling tip.

About the specificity of the nanostructures: the crucial role of dynamization

The demonstration of the specificity of the structure of NS towards the nature of the remedy, especially in the ultramolecular range, should constitute a key-point for the acceptance of homeopathy; in other words, are the solute-induced NS distinguishable between two different solutes? Rey managed to show differences in the thermoluminescence profiles of C15 NaCl and C15 LiCl in D2O [76]. Demangeat [47,77] using NMR relaxation, managed to differentiate

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non ultramolecular high dilutions of histamine from manganese/lactose prepared simultaneously in the same batch of solvent, and to confirm this result with ultramolecular dilutions of histamine and arsenic/lactose. Interestingly, NMR differentiation could only be observed if the dilutions had been dynamized [47]. This important finding was recently reproduced with Cuprum and Gelsemium using the same NMR technique [49]. The authors concluded that the "specific signature" of the homeopathic remedy is due to the dilution/dynamization process probably due to the formation of mesoscopic water structures around NPs and/or NBs. The crucial role of dynamization, already shown on Figure 2, can be clearly illustrated on Figure 5, too.

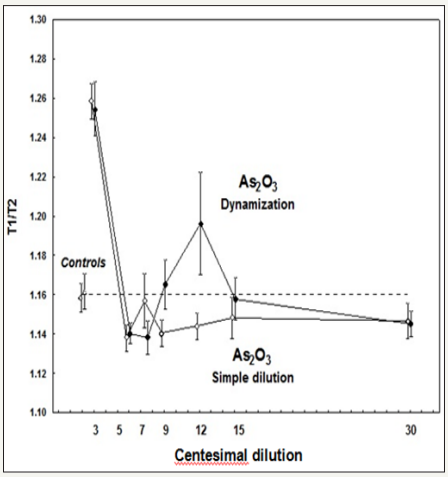

Figure 5: Effect of dynamization versus gentle manual agitation for the preparation of arsenic (As_2O_3) dilutions [47]. The preparations were carried out simultaneously in the same batch of water. Upon dynamization, a drastic change was observed with emergence of a pseudo-oscillatory profile (p=0.015 within the C9-C15 range). It is tempting to connect this behavior to the known non linear, even oscillatory, biological effects of successively higher potencies, especially of arsenic dilutions [64,125].

Recent advances confirming the presence of NPs in high dilutions

Chikramane et al. [78] demonstrated for the first time by Transmission Electron Microscopy (TEM) the presence of NPs in commercial ultrahighly diluted (C30 and C200) metal-based homeopathic medicines. Since then, many studies did confirm these findings, using various techniques for visualization and characterization, among them high-speed videography, TEM, Scanning EM, Nanoparticle Tracking, DLS, Zeta potential, Selected Area Electron Diffraction, Energy Dispersive X-ray Spectroscopy, Inductively Coupled Plasma Mass Spectroscopy [33,38,39,44,79-86]. In these studies, NPs ranging from 1-2nm to several tens and even hundreds of nanometers were shown in various homeopathic medicines (metals, inorganic salts, plants), at all levels of dilution up to C30, C200 and beyond C100.000. Sizes appeared very discordant, of the order of 1-15nm [33,82,83,85], 90nm [81] and 150-300nm [80,84] for the same (C6) level of dilution. The discrepancies may be attributed to the mode of preparation. Indeed, most studies were carried out using commercial dilutions from Indian manufacturers, with none or little details of preparation [38,39,78,80,82,84-86], and with 90-95% ethanol as medium. Since metal NPs and inorganic salts were prepared using trituration in lactose, and diluted in ethanol, the low solubility conditions might have induced precipitation and even crystallization of the lactose [87]. In this highly controversial field, procedures should be precisely described. Laboratory research studies should be preferred, with proper controls, as was the case for some [33,44,79].

At electron microscopy, NPs were shown to grow with increasing dilution between C4 and C30 [33], C30 and C200 [78], C6 and C50.000 [82]. In some studies, NPs showed increasing sizes between C6 and more than C100.000, but with fluctuations of sizes or shapes [39,83]. On the other hand, decreasing sizes were reported between C6(150-300nm), C30(60-170nm) and C200(10-100nm) [80,84]; but it is worth pointing out that the starting sizes in those studies were very large so that the observed decrease could merely reflect a fragmentation during dynamization.

Strikingly, NPs were also observed in some commercial control solutions from Indian manufacturers [38,81]. A study conducted in a European laboratory also showed that dilutions/dynamizations of lactose as controls contain 1-2nm-sized NPs [33,34]. Noteworthy, dilutions of Cuprum metallicum C30 and of Aqua pura C30 as control, prepared through trituration with lactose, showed NPs of the same composition in C, O, Si, Na and Ca elements that reflected both the initial presence of lactose and the release of material from the glass. A significant higher level of silica at C30 than at C4, in dilutions and in controls, confirmed an iterative leaching process from the glass. Moreover, the authors studied several types of source material (Cu, Au, KCl, Gelsemium) and were able to discriminate the shapes of NPs, not only between a metal, a salt and a plant, but also between different metals and between different levels of dilution.

Some TEM findings support the assumptions made above concerning the nature of NS and the mechanism of their transfer across dilutions. Temgire et al. [39] reported that NPs appeared encapsulated within a silicate coating containing entrapped NBs and postulated that NBs around the coated particles, through attachment to larger bubbles, could be involved in a levitation process as described by Chikramane [44] to ensure the transfer of material across dilutions.

It has been shown above that nanostructures only appeared beyond a dilution of 10^{-5}-10^{-7} [19,26,51]. It is obvious that this assertion is no more valid when starting materials are nanoparticles themselves, what is the case for most studies quoted in this section: synthesized NPs, metals, raw inorganic salts diluted in ethanol along with lactose trituration, and especially mother tinctures of plants provided by industrial manufacturers, which are complex media, not chemically characterized and able to synthesize NPs in presence of salts of metals [88]. Nevertheless, the mechanism postulated above, implying NBs to explain the growth of superstructures and their transfer across the successive dilutions, remains valid for NPs as source material.

About the question of remnant remedy in extreme dilutions

Answering this question is likely to bring credibility to homeopathy. For about 15 years, many reproducible studies in various fields of physicochemistry clearly demonstrated the persistence of residual physical signals in ultrahigh dilutions, beyond the threshold of Avogadro: thermoluminescence [76,89,90], NMR relaxation [35,36,42,49,91], UV spectroscopy [92], microcalorimetry, pHmetry and conductometry [93-96]. Since 2010, more direct arguments could be brought, especially from electron and X-ray diffraction, and inductively coupled plasma mass spectroscopy. Chikramane et al. [78] reported for the first time measurable remnants of starting material (metals) in commercial ultrahigh dilutions up to C200. In a subsequent study, from their own controlled preparations, they could establish that extreme dilutions reach a non-zero asymptote, at about 100-200ng/mL, starting from C6 [44]. However, their procedure required an unusual technique of dilution, i.e. sampling from top layers of liquids. Several other studies identified, too, remnant material in ultramolecular dilutions, far beyond C30 and C200 [39,82-85]. Curiously, increasing amounts of remnant material were found with increasing dilutions, between C6, C30, even C200 and beyond [78,83-85]. Other studies could unequivocally identify NPs in ultrahigh dilutions but did not manage to demonstrate the presence of starting material [33,81]. Surprisingly, in a study of Cuprum metallicum triturated with lactose, the copper element could not be identified beyond C4, but lactose remained detectable up to C30 [33]. Discrepancies among studies may be due to limits of instrument detection, or to artifacts. It should indeed be pointed out that the EM technique itself may create artifacts by the prior sonication of the dilutions if any (likely to release silica and produce NPs), or by the pre-concentration and evaporation processes (likely to produce aggregates on the TEM grid) [97]. And the analysis of elemental composition of NPs by diffraction techniques clearly reveals contamination by the elements of the grid [39]. In fine, if the existence of NS/NPs in high homeopathic dilutions appears to be attested by numerous studies, the presence of remnants within these remains to be established definitively, despite a set of appealing arguments.

Transfer onto sucrose globuli

A last important question is: Do nanosized superstructures survive after being poured onto sugar globuli, as commonly used in clinical practice? Strong indirect arguments have been brought by Lenger et al. [98,99] using delayed luminescence and by Klein & Wolf [100,101] using UV-spectroscopy, to differentiate ultrahigh dilutions of various remedies on sugar globuli from the control globuli. Recently, Electron Photonic Analysis, a very sensitive and specific technique, has been applied to the detection of material directly on the globule with convincing and promising results [34]. Especially, globuli impregnated with Cuprum metallicum and Gelsemium could be clearly distinguished, as well as samples aged of tens of years from the reference and from fresh samples.

Part 2: Hypotheses on the Biological Activity of Homeopathic Remedies

At low dilution

At low dilution, below 10^{-5}, or 10^{-4}-10^{-6} (C2-C3) depending on the substance, the solution may behave in a standard manner. The presence of the source molecule in the dilution would ensure a specific "molecular" action at the level of receptors, in a manner analogous to classical pharmacology. This is in agreement with the view of Bellavite et al. [64,67] who claimed that the specificity of any drug is based on the interaction of active principles with their biological targets (enzymes, cell receptors, membrane channels, transcription factors in gene expression), and that the same is conceivably true for homeopathic drugs. These authors could show changes in the expression of key genes, mainly cytokines, receptors and transcription factors, induced by the homeopathic remedies Gelsemium sempervirens and Arnica Montana, likely to understand their anxiolytic, anti-inflammatory and wound-healing bio-effects, observed in clinical practice [102,103]. Significant effects were found essentially with the lowest dilutions (C2-C3). On the contrary, some paradoxical inverse effects were observed at high dilution (C15-C30); this will be discussed below.

At high dilution

Beyond a dilution of $10^{-7,}$ or 10^{-6}-10^{-8} (C3-C4) depending on the substance, the molecules of the remedy source are no more in a "molecular" state, but appear included within NS or NPs, with a wide variety of sizes from 2-3nm up to hundreds of nanometers. The NS grow, or even fluctuate, with dilution, as demonstrated by many findings reported throughout this paper. These NS/NPs, containing the active substance in their core, are transferred from dilution to dilution. It will be postulated, from several direct and indirect findings-however without definitive proof-that the remedy could be transferred up and far beyond the Avogadro's limit. So, superstructures would behave as vehicles for the active ingredient. Several in vitro [80,84,86], (review in [104]) and in vivo studies (review in [105]) clearly support the biological activity of NPs in the ultramolecular range up to C200 with the highest effect at C200 in one study [80]. Marzotto et al. [102] showed modifications of gene expression in human neurocytes by dilutions of Gelsemium up to C30, in which, from another study, NPs have been identified [33]. NPs have many peculiar physical and biological properties and thus are nowadays a subject of intensive research [65,66,69-71,74,75,86,106-120]. Briefly, they enter cells and nucleus easily-where they can induce epigenetic perturbations [117]-in contrast

to small molecules and biological molecules; they cross skin, lung and blood-brain (BBB) barriers, and have large specific surface areas for adequate binding and biological interactions, resulting in a drastically enhanced reactivity.

It was recently shown that homeopathically prepared C30 to C200 dilutions of various metals (at fg/mL), unequivocally containing NPs, had a billion-fold higher action compared to studies using synthetic NPs (microg/mL) [86]. NPs enter human body via inhalation, ingestion and dermal penetration, travel by lymph, blood, and also by olfactory and trigeminal nerves to directly reach the central nervous system-through the olfactory bulb (OB)-and the centres which regulate the autonomous nervous system [106,108,113,121-123]. The olfactory pathway and olfactory receptors have even been proposed as a main portal of entry and target for homeopathic nanomedicines (Courtens et al. "Could the olfactory system be a target for homeopathic remedies as nanomedicines?" under submission). The bioavailability and membrane permeability greatly depend on the size, shape and charge surface. It has been postulated that NPs less than 100nm can enter the cells and the axons and dendrites of neurons, less than 40nm can enter the nucleus and smaller than 35nm can cross the BBB [109]. Very large NPs (more than 500nm) are eliminated through mucociliary clearance, but NPs of the order of 100nm or more may activate the immune system, following any route of uptake: nasal associated lymphoid tissue, respiratory and digestive mucosae, microglial cells of the OB (reached via the olfactory pathway) [75,110,113]. Interestingly, OB microglial cells play a pivotal role and serve as sensors and/or modulators of immune responses and inflammatory events in the brain, by releasing pro-inflammatory factors [112,113,119,120] which can act on the pituitary axis [118]. So, according to their size, NPs may induce various biological responses. Moreover, silica is a well-known cellular stressor and adjuvant (even homeopathic high dilutions of silica were shown to induce stimulation of peritoneal macrophages [124]); its presence within NPs make them not only conveyors of the remedy, but also non specific amplifiers of the cellular response to the specific source remedy, as proposed by Bell et al. [65,66].

The Paradox of Homeopathy

Differential biological actions of low and high dilutions

In clinical practice, low dilutions are effective for local disorders whereas higher ones are effective for general, systemic and psychic symptoms. Dilutions below C2-C3, still containing molecules in ponderable and subponderal quantities, would bind at an "organ level" to receptors and cellular specific targets as conventional remedies do. Above C3-C4, the nanoparticulate form of the remedy, the size of which generally increases with dilution, could explain why the higher the dilution, the more systemic, intense, rapid and sometimes long-lasting is its action. A direct access to the immune system, to the central and autonomous nervous systems, to the pituitary axis, via the BBB or the olfactory pathway allows the remedy to bypass organ cellular reactions and trigger a systemic reaction. Too, NPs may bypass membrane receptors and trigger epigenetic effects at the nucleus level of the target tissues. Long-lasting effects could be explained either by retention of NPs in some organs and interstitial tissues, or by epigenetic changes which can be very stable [117].

Oscillatory biological activity at high dilution

The activity of successive high dilutions, essentially beyond the Avogadro's limit, may show a periodicity of sinusoidal type (Figure 1), sometimes so remarkable that Demangeat [54] speculated on a physical origin, and foremost arising from the preparation of the dilutions. Many years ago, Barnard and Stephenson [20] explained this phenomenon by the formation of chains of water polymers-bearing the "Memory of water"-which grow with dilution to a point of rupture due to shear forces; thus, during the successive dilutions, the average molecular weight of these chains oscillates between a minimum and a maximum value. Such a mechanism could be transposed here: NS or NPs grow at each step of dilution, then collapse after critical magnification and reform in the subsequent dilutions, and so on, with almost perfect mechanical regularity. This hypothesis is supported by some EM findings reported above [50,51,83] and by the experiment described in Figure 5.

It can be speculated from all these observations that the true factor of biological activity could be the number of dilutions/dynamizations-which determines size, bioavailability and bioreactivity of NS/NPs-rather than the residual concentration of the active principle in the dilution, possibly present at a non-zero asymptotic level. A recent study from Betti et al. [125] supports this idea. They showed that the number of succussions (N), applied for the preparation of an ultramolecular decimal dilution of arsenic (D45), affected the in vitro wheat germination (stimulation for N=4 and N>32; inhibition for N=8 and N=16), and induced growing polycrystalline structures above N=32. The number of succussions within a definite dilution may thus modulate the biological activity. A mathematical approach has been built establishing the relationship between sizes of information-carrying units, number of succussions and dilution factor, leading to a plausible interpretation why potencies at regular ratios are traditionally used in the clinical practice [126].

Inverse effects

The dilution range 10^{-4}-10^{-8} (C2-C4) corresponds to the transition between molecular and nanoparticulate forms of the remedy. This range appears quite peculiar with epiphenomena observed in biology as well as in physicochemistry. Paradoxical effects are known in toxicology since the last decades of the 19th century (hormesis, i.e. adverse effects at high doses and beneficial effects at low doses) and are now recognized in many drugs by modern pharmacology [63]. However, the relationship to homeopathy is a matter of conflicting debates [64,68]. In order to explain inverse effects at the cellular level, Bellavite et al. [67] proposed a very attractive mechanism of allosteric regulation. Similar ligands can bind at the same allosteric site, with one acting as an agonist and the other as antagonist; the chemical difference between allosteric agonists and antagonists can be small; the

authors suggested that dynamization may induce such small changes in the physicochemical nature of the active principles. According to this idea, the onset of hormetic effect in the 10^{-4}-10^{-8} range might correspond to the onset of the nanostructural form of the remedy. In the study of arsenic D45 on wheat germination reported above [125], an inhibitory effect was observed for 8 and 16 succussions, and a stimulating effect for more than 32 succussions; strikingly, this threshold corresponded to the onset of well-organized polycrystalline structures observed in the dilutions. In the study of Gelsemium and Arnica [102,103], inverse effects in the expression of genes were unexpectedly found at high C15 and C30 dilutions, compared to the normal, expected effects at low dilution. Chikramane et al. [86] using MTT, recently reported hormetic effects by homeopathically diluting-by successive factors of 1/3 and 1/10-high dilutions (C6, C30, C200) of metal NPs as starting solutions. This finding corroborates that of Betti et al. [125] reported above. It demonstrates that whatever the initial dilution, even ultramolecular, subsequent dynamizations or subsequent dilutions/dynamisations induce reverse biological activities. This might reflect allosteric-type mechanisms related to changes in the 3D-conformation of the superstructures due to dynamization. Homeopathic biological and physicochemical research could benefit from focusing on the effect of either varying the number of dynamizations, or serially diluting (by a factor 1/10 or less, but not 1/100) a definite subponderal or ultramolecular dilution, in order to evidence biological or physical fluctuations around the starting dilution.

A different explanation of inverse effects has been proposed by Bell et al. [65,66]. NPs would act not by direct pharmacological effects on receptors, but as biological signals (stressors) that stimulate the organism's allostatic biological stress response network. In other respects, in the fields of pharmacology and toxicology, where conventional procedures of manufacturing are used, paradoxical aggregation of solutes upon dilution (reported in [51,55]) could mimic formation of NS and thus explain hormetic effects.

Conclusion and Prospects

Homeopathic dilutions differ from conventional dilutions of physicochemistry. The specific dilution/dynamization procedure induces collateral phenomena, especially production of NBs and release of silica and ions from the glass container, which lead, at high dilution beyond C3-C4, to the formation of nanometric superstructures or NPs stabilized by internal and/or coating silica. It has been here emphasized the fundamental role of dynamization and of NBs which ensure the formation and growth of the nanostructures, their stereospecificity, their transfer across dilutions, and their enhancement and/or regeneration by a second dynamization. It has been hypothesized, from NMR studies, a structural duality of the homeopathic remedy, likely to explain the differential and paradoxical actions recognized by the medical practice. The remedy, in the "molecular" form at low dilution would act on organ molecular targets through ligand-receptor interactions, as conventional medicines, and on systemic targets (immune, endocrine, nervous) and transcriptional function at high dilution, due to the peculiar properties of its nanoparticulate form.

Undoubtedly, homeopathic solutions can no more be considered as pure water. Numerous studies in physics and EM attest the presence of nanoparticulate material in very high homeopathic dilutions, even far beyond Avogadro's limit. However, although many studies do suggest it, the residual presence of the initial ingredient in the ultramolecular dilutions remains to be proved, as the question of contamination cannot be ignored [127,128]. But if this was definitely established, the notion of "Memory of water" would definitively lapse. Homeopathy would then be reduced to microdose pharmacology, exhibiting hormetic-type responses which justifies the simile therapeutic principle [129], and would be included in the present panoply of nanomedicine. Research in this field has accelerated in recent years; efforts should focus on confirming first the hypothesis of the residual presence of the remedy in ultramolecular dilutions (this could be achieved quickly with current high-performance analytical methods), and second the crucial role of the dynamization process, as it will probably emerge that the true factor of the biological activity of homeopathic remedies is the number of dilution/dynamization steps applied to reach a given dilution level, or the number of succussions applied within each step. The use of decimal dilution and of various levels of dynamization could reach the same biological activities as ultra highly centesimal dilutions, while staying below the limit of Avogadro and thus conferring a more rational character to homeopathy.

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