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Adaptive network nanomedicine: an integrated model for homeopathic medicine

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1. ABSTRACT

This paper presents an evidence-based model for the nature and mode of action of homeopathic remedies. Recent studies reveal that homeopathic remedies contain nanoparticles (NPs) of source materials formed by "top-down" mechanical grinding in lactose and/or succussion (forceful agitation) in ethanolic solutions. Silica nanostructures formed during succussions in glass and/or biosynthesized by specific plant extract tinctures also may acquire and convey epitaxial information from remedy source materials into higher potencies. NPs have enhanced bioavailability, adsorptive capabilities, adjuvant reactivity, electromagnetic and quantum properties compared with their bulk forms. NPs induce adaptive changes in the organism at nontoxic doses (hormesis), serving as salient, low level danger signals to the biological stress response network. Activation of stress response effectors, including heat shock proteins, inflammasomes, cytokines and neuroendocrine pathways, initiate beneficial compensatory reactions across the interconnected networks of the organism as a complex adaptive system. Homeopathic remedies act by stimulating hormetic adaptive rather than conventional pharmacological effects. Updating terminology from "homeopathy" to "adaptive network nanomedicine" reflects the integration of this historical but controversial medical system with modern scientific findings.

2. INTRODUCTION: FROM HOMEOPATHIC MEDICINE TO ADAPTIVE NETWORK NANOMEDICINE

Homeopathy is a more than 200-year-old whole system of complementary and alternative medicine (CAM) (1). Despite historical skepticism of the field from mainstream medicine, homeopathic medicines (remedies) are used by approximately 500 million people worldwide (2) as a low-risk treatment approach for acute and chronic conditions, though utilization rates vary markedly from country to country (3, 4). In recent decades, homeopathy has developed a growing basic science, clinical, and health services research literature showing unique physico-chemical properties, biological activity *in vitro* and *in vivo*, good real-world effectiveness, exceptional safety, and, in many studies, cost-effectiveness (5-10).

However, skepticism and uncertainty about the nature of the remedies and their mode of action has slowed more widespread acceptance and utilization of homeopathy in integrative medicine. Skeptics keep returning to their belief that homeopathic remedies per se cannot exert any effects other than placebo effects. That is, homeopathy is claimed to be "implausible" on "scientific" grounds (11), which revolve around a focus on the serial dilution component of remedy manufacturing. Typically skeptics selectively ignore the basic science and preclinical data,

Table 1. Core elements of the nanoparticle-cross-adaptation-sensitization model

Core Element	Implications
Homeopathic medicines are source nanoparticles (NPs) generated by mechanical top-down methods (triturating or grinding in lactose; succussing or agitating with turbulent mixing in ethanol-water solutions) (60, 61, 63, 64, 72, 74, 101, 106) and adsorbed to other source NPs, lactose, and/or silica NPs	Increase in • Adsorption of other NPs onto their highly-reactive surfaces (83, 84) • Bioavailability and bioactivity at reduced doses compared with bulk forms of source (77, 89, 90) • Access to cells (91) • Capacity to activate cellular defense systems of the body, e.g., inflammasomes, cytokines, heat shock proteins (47, 52-54, 68, 170, 174, 220) • Catalytic activity (84) • Acquired electromagnetic, magnetic, thermal, optical, quantum & other properties not found in bulk forms of source (83, 84, 116, 118, 162, 163, 278)
NPs initiate hormesis (69), an adaptive process of the organism as a whole	Salient, nontoxic NP low doses serve as mild systemic stressors and initiate organism-based adaptive, endogenously amplified (sensitized by immune (68, 170) and/or nonimmune (197, 252) mechanisms) changes in multiple functions to prepare for future encounters with or recover from past encounters with higher doses (intensities) of the same or a cross-adapted substance or stressor(s) (69, 190)
Hormetic adaptations engage biological metaplasticity and plasticity processes in the stress response networks of the organism as a complex adaptive system (184, 186, 193, 205)	Homeopathic NP-initiated healing reflects a sudden self-organized critical phase transition in pattern and direction of global and local function (202) from disease-generating "stuck" (279) dynamics to healthier, more flexible and resilient dynamics (280) as emergent processes of the organism

discount any positive clinical studies (12, 13) and point to the more mixed placebo-controlled, double-blind randomized clinical trial literature and one flawed meta-analysis dependent on 8 homeopathy trials (12, 14) as definitive "proof" that this entire field is invalid (13). Patient-provider factors are an emerging focus of clinical study in homeopathy (15-17).

On the other hand, CAM investigators emphasize significant problems of poor external and model validity in applying conventional clinical trial designs to study homeopathic treatment (18-20). For instance, one large study of homeopathically-prepared, but not homeopathically-prescribed, dust mite 30C medicine in asthmatics revealed the seemingly paradoxical finding that verum and placebo groups were not clinically different after a 16-week trial (21), but the pattern of changes in the verum group over time was oscillatory and distinct from the flatter response pattern in the placebo group (22). Observational studies on thousands of homeopathic patients suggest improvement rates that can range between 60-90%, with earlier improvements in acute illnesses compared with standard of care, reduction in concomitant symptomatic medications, and associated cost-savings in many studies (5, 6, 23-26). Objective sleep and waking electroencephalographic studies indicate that homeopathic remedies exert measurable nonlinear effects different from placebos in human subjects and animals (27-36). Multiple *in vitro* studies demonstrate that remedies can evoke complex patterns of changes in immune, inflammatory, oxidative stress, and biological signaling pathways (8, 9, 37-58).

A clearer understanding of homeopathic remedies and their mode of action would assist scientists in putting the total research literature into better context and in designing more appropriate future studies. Homeopathic clinicians would be able to practice clinically-relevant evidence-based care. Taken together, the available scientific evidence now points to a testable comprehensive model for the nature of homeopathic remedies and their interactions with living systems (59). The empirical data indicate that "something" is indeed happening when a cell or organism encounters a homeopathic remedy. Despite the seemingly confusing body of observations, three broad research literatures coalesce to provide a scientific explanatory model, i.e., (a) the properties of nanoparticles (NPs); (b) the biology of the stress response; and (c) the complex adaptive network nature of the organism as a whole. The purpose of the present paper is to summarize this evidence-based understanding of the nature of homeopathic medicines and how they act.

The core elements and implications of the Nanoparticle-Cross-Adaptation-Sensitization model are summarized in Table 1. Evidence indicates that homeopathic remedies prepared in serial dilutions with initial trituration (mechanical grinding) and/succussion (intense agitation of ethanolic solutions) contain nanoparticles of their source materials (60, 61). Other lines of evidence suggest that plant (62) and other source materials can adsorb onto the surface of silica, polymer, or other nanoparticles previously shown to result from the succussion process (63, 64). NPs trigger local biological signaling events in the stress response pathways that defend against exogenous dangers and mobilize the global living system to adapt as an interconnected complex adaptive network (65-68). In small quantities, NPs stimulate adaptive changes across the organism without exerting damage, i.e., hormesis (69, 70). The remainder of the paper discusses each element in greater detail below to provide the scientific foundation for reconceptualizing homeopathic medicine as adaptive network nanomedicine.

3. HOMEOPATHIC MEDICINES AS "TOP-DOWN" NANOPARTICLES

3.1. Overlaps between homeopathic remedy manufacturing and nanoparticle manufacturing methods

Homeopathic medicines or remedies contain crude nanoparticles, nanoaggregates, and/or nanocrystals of their original source substance (60, 61). The starting point of the model is that homeopathic remedies are nanoparticle (NP) forms of their source material because of the ways in

Table 2. Nanoparticle (NP)-related studies using homeopathic remedies

Homeopathic Remedies	Remedy Potencies	Comments	Reference
Gelsemium	Mother tincture to 12C	• Glass vs polypropylene containers produced different properties • Hand jerk succussions vs sonication vs vortexing produced different properties	(63)
Gelsemium	Mother tincture encapsulated with poly(lactide-co-glycolide) NPs	• NP form was more potent than bulk form in inducing apoptosis of A375 cells	(76)
Hypericum	Mother tincture used to biosynthesize gold NPs	• NP form at 20 mg/kg produced similar effects as bulk form at 200 mg/kg in restraint-stress induced behavioral and oxidative damage of mice	(77)
Phytolacca	Mother tincture used to biosynthesize silver NPs from silver nitrate	• Silver NPs had anticancer and antibacterial, but not antifungal properties	(62)
Phytolacca Gelsemium Hydrastis Thuja	Mother tinctures used to biosynthesize silver NPs from silver nitrate	• Silver NPs made with different plant tinctures exhibited different physico-chemical properties, antiproliferative effects, antibacterial activities	(113)
Aurum metallicum Argentum metallicum Platinum metallicum Stannum metallicum Cuprum metallicum Zincum metallicum	6C, 30C, 200C	• Metal source NPs were observed using transmission electron microscopy, persisting at all potencies • NP quantities differed between manufacturers and between batches within the same manufacturer	(61)
Belladonna Colchinum Pulsatilla	1C to 15C	• Nanoparticles and crystalline aggregates rich in silicon were observed using transmission electron microscopy at all potencies	(60)

which they are manufactured from bulk form substances (61, 63). Remedy manufacturing begins with mechanical milling and grinding (trituration) in lactose and/or vigorous agitation in ethanol-water solution by manual pounding of the container on a hard elastic surface (succussion), vortexing, or sonication (44, 63, 71). Classical remedy preparation uses glass containers, though some contemporary manufacturers may employ polymer containers of polypropylene or polyethylene (63). Table 2 lists studies involving homeopathic remedies and nanoparticles.

Mechanical milling (72), sonication (73), microfluidization and flash nanoprecipitation (74), and using botanical extracts (75), including homeopathic plant tinctures (62, 76, 77), for biochemical catalysis and NP generation are among a variety of ways in which modern nanotechnologists make nanoparticle forms of source materials. The intense bidirectional fluid turbulence during succussion would cause particle collisions and shear off smaller and smaller particles from the bulk starting material, as well as generate nanobubbles (78). In turn, nanobubbles create tiny areas of localized high temperatures and pressures to shear off additional smaller nanoparticles from larger source particles and perhaps silicates in solution (64, 79-82), leading to their uneven distribution in colloidal solutions (82). In parallel with homeopathic trituration and succussion, combining wet grinding with sonication in nanotechnology is more effective than grinding alone or sonication alone in limiting nanoparticle aggregation that otherwise occurs in solutions (73).

Nanoparticles (NPs) are small particles of source material with at least one dimension measuring less than 100 nanometers (83, 84). Ethanol as a solvent tends to foster generation of relatively smaller-sized nano-structures during ultrasound treatment of solutions (82). This point has clinical implications, as some smaller NPs tend to be more toxic than larger NPs, including nanosilica and nanopolystyrene (85-87). In addition, NPs are generally much more bioavailable than their respective bulk forms (76, 77, 83, 88-91). Thus, to use the extensive variety of source NPs that homeopaths utilize safely in therapeutic applications (6), very low doses are indicated. In fact, many studies of nano-forms of herbs, nutriceuticals, vaccines, and drugs suggest that doses can be 10 to 1000 times lower than typical bulk form doses to produce the same direct biological effects (77, 89, 90, 92, 93). To minimize direct adverse effects (70, 94) but still mobilize beneficial endogenous adaptive responses (69, 95, 96), nanomedicine doses need to be very low (70, 97-100).

Modern nanotechnologists make nanoparticles and nanocrystals in one of two ways – by "top-down" mechanical milling or grinding methods (72, 101, 102) or by "bottom-up" molecular self-assembly (103). The top-down process for making nanoparticles from bulk form materials was first developed in modern nanotechnology in 1966 (72). One company, Elan Drug Technologies, even patented a top-down drug milling method named "NanoCrystal®." The purpose of this approach for nanomedicine is to improve bioavailability of otherwise poorly soluble drugs (101, 102, 104, 105) reportedly by as much as 600% (http://ir.elan.com/phoenix.zhtml?c=88326&p=irol-newsArticle&ID=1365330&highlight=, accessed 8/03/12).

Notably, mechanical milling of lactose will itself generate complex nanocrystalline and other nanostructures of the source sugar (106). Succussion in glass generates small but measurable amounts of biologically active silica from the walls of the container (64). The heightened capacity of nanoparticles for adsorbing other materials onto their surfaces has been shown for animal serum albumin

with both lactose (107) and silica (108). Thus, lactose (106) and/or silica (109) nanoparticles may be "nanocontaminants" in most homeopathic remedies, depending on potency, potentially serving as nanoadjuvants to stimulate heightened reactions to remedy source particles (cf., (89)) and drug delivery vehicles to reduce dose levels (77, 110, 111). If the remedy is succussed in a polyethylene rather than glass tube, other data suggest that the container releases nanoparticles of the polymer into the colloidal solution (63).

During the 1800's, Samuel Hahnemann, MD, the physician-chemist who founded homeopathy, originally described a manual method of drug grinding and turbulent fluid agitation with ethanol-water solutions in small glass containers (71). Hahnemann pointedly emphasized the essential role of trituration requiring prolonged intense mechanical grinding of source material in lactose with mortar and pestle, per step and succussions (many repetitions of violent manual pounding of the liquid solution in a glass container against a hard elastic surface), for generating active homeopathic remedies. In his book, the *Organon of Medicine 6th edition*, completed in 1842, he observed (71): *"…This remarkable alteration in the properties of natural bodies is achieved through mechanical action on their smallest particles by trituration and succussion while these particles are separated from one another by means of an intervening, indifferent substance that is either dry [e.g., lactose] or liquid [e.g., ethanol-water solution] …Likewise, rubbing a medicinal substance and succussing its solution (dynamization, potentization) develops the medicinal powers lying hidden in the medicinal substance and discloses these powers more and more…"*

Skeptics of homeopathy mistakenly focus on the serial dilution steps that are also performed in making homeopathic remedy potencies, e.g., with dilution factors of 1 part source in 10 parts diluent (X potencies) or 1 part source in 100 parts diluent (C potencies). They claim that such dilutions render a solution no different from plain water. Even Hahnemann agreed with this point with regard to bulk form materials (71). Dilution without trituration and/or succussion, i.e., to make small medicinal particles, does not make a homeopathic remedy. Clearly, modern NP manufacturing methods are more sophisticated than those used in classical homeopathic manufacturing, but they are nonetheless all procedures that can generate nanoforms from bulk form materials.

3.2. Basic science findings on homeopathic remedies

In contrast with the misleading assumptions of skeptics about dilution, the nanostructured nature of triturated and/or succussed homeopathic remedies has empirical support (9, 60, 61, 63, 76, 106) (Table 2). For example, using transmission electron microscopy, Chikramane *et al* (61) demonstrated that source nanoparticles persist in six different commercial homeopathic metal remedies from two different manufacturers, at liquid potencies of 6C, 30C, and 200C (where C potencies mean a dilution factor of 1 part source to 100 parts diluents per step, with initial trituration and 10 or more successions after each dilution step). The metal remedy preparation involved both initial trituration in lactose and subsequent dilutions and successions in ethanol-water solutions within glass containers. With ordinary dilution of bulk materials, conventional pharmacological principles suggest that no active source material should remain in homeopathic remedies higher than 24X or 12C, i.e., past Avogadro's number of molecules (6×10^{23}). Nonetheless, biological activity does persist (9, 112).

Trituration alone, even without succussion, using traditional methods for sampling part of each "dilution" in order to make the next successive dilution, also generates biologically active homeopathic remedy at potencies up to 200C (44). Conversely, succussion alone using ethanolic plant mother tinctures without initial trituration, produces remedy source NPs. Upadhyay and Nayak (60) reported finding source nanoparticles and crystalline aggregates as well as silicon in three different plant remedies made from mother tinctures into homeopathic potencies from 1C to 15C. The latter researchers pointed out the possibility that the silicon/silica in the nanostructures succussed off the walls of the glass containers could carry specific remedy source-modified structural information into higher potencies.

Remedy source materials could adsorb onto and modify lactose or silica nanoparticles even upon their initial formation in the 1C or 1X preparation step (Figure 1). Using four different homeopathic plant mother tinctures, i.e., concentrates, to synthesize silver nanoparticles, Das et al observed subtle but detectable differences in the sizes, physical characteristics and biological properties of the resultant silver NPs (113). If specific remedy source materials in homeopathically-prepared medicines similarly modify silica NPs and crystallites from the glass container at lower potencies, the resultant nanostructures could acquire, seed, and convey a persistent silica-based structural "memory" of source information at higher potencies (60, 64). Silica can not only carry other nanomaterials per se, but also self-assemble "bottom-up" nanostructures using DNA, proteins, crystals or living cells as epitaxial templates (114) (Table 3). Plant extracts can biocatalyze formation of oligomers and/or aggregrated silica nanostructures from very small silica nanoparticles in aqueous solutions at room temperature (115).

Furthermore, data from Raman and UV-vis spectroscopy as well as fluorescence spectroscopy, tools used to characterize nanomaterials, also show that specific homeopathic remedies differ from one another and from plain solvent controls (63, 78,). Like other types of nanoparticles (84, 116-118), homeopathic remedies also differ from controls in their thermal, electrical, and optical properties (119-122). Like NPs (84, 118, 123), homeopathic remedies may also exhibit quantum macroentanglement-like characteristics under certain experimental conditions (124). Consistent with the nonlinear dependency of NP properties on particle sizes, shapes, and quantities (70, 84-87, 90, 94, 108, 125, 126), homeopathic remedies exhibit more variability in their effects than conventional bulk form drugs (5). The

Table 3. Proposed nano-forms, relevant homeopathic manufacturing processes, and roles in remedy effects

Nano-form	Relevant Homeopathic Manufacturing Process and Comments	Proposed Role(s) in Remedy Effects
Nano-lactose (106,107)	• Trituration of specific remedy source material in lactose • Longer duration and higher force of grinding may generate smaller nanoparticle forms and crystals	• Drug delivery vehicle for adsorbing, carrying, and delivering remedy source at lower potencies
Nano-silica (60,64)	• Succussion of specific remedy source material in ethanol-water within glass container • Method, force, numbers of succussion will modify resultant nano-silica structures, sizes and amounts generated (63) • Size of container and type of glass will modify resultant nano-silica structures, sizes and amounts generated (63, 64) • Preparation with certain remedy sources (plant tinctures and sponges) may lead to biosynthesis of additional nano-silica structures retaining remedy source-specific information (113, 115) • % ethanol will modify resultant sizes and properties of nanoforms (82)	• Drug delivery vehicle for adsorbing, carrying, and delivering remedy source material in liquid potencies (91) • Epitaxial bottom-up self assembly of nano-structures from template of remedy source material NPs, DNA, proteins, cells – serving as remedy-specific structural information carriers that could survive drying and interact with living cells (114) • Nano-silica by itself will serve as a non-specific adjuvant to activate enhanced biological defenses in immune and inflammatory networks (65, 170, 174)
Nano-remedy source (60,61, 101, 113)	• Succussion of specific remedy source material in ethanol-water within glass container • Method, force, numbers of succussion will modify resultant nano-remedy structures, sizes and amounts generated (63) • Size of container and type of glass will modify resultant nano-remedy structures, sizes and amounts generated (63, 64) • % ethanol will modify resultant sizes and properties of nanoforms (82)	• Salient remedy nano-forms will stimulate hormetic biological adaptive responses to the low level remedy stressor as an organism-specific perceived threat (52-54)

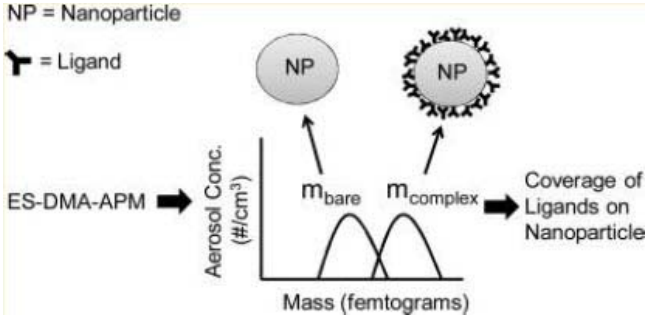

Figure 1. Ligand Adsorption to Nanoparticle Surfaces. In the current model, remedy source, lactose, and silica particles and crystals would adsorb onto one another in nanosized structures to convey remedy-specific materials and/or structural information during remedy preparation and administration. Initial remedy preparation by trituration and succussion would mechanically shear off smaller particles in a a top-down manufacturing process. As more nanosilica is formed and released over the course of successive dilution and succussion steps, a bottom-up self-assembly process might occur in which nanostructures of silica form around the remedy source materials as seed templates and also carry the "memory" of their structural information into higher potencies and interact with the organism's cells. ES-DMA-APM (electrospray-differential mobility analyzers and particle mass analyzer) is one technique for quantifying ligand adsorption to nanoparticles. Reproduced with permission from reference (132).

enhanced bioavailability (76, 88, 91) and biological reactivity (83, 89, 90) of NPs, like homeopathic remedies (38, 45, 47, 55, 57, 58, 77, 127-129), enable the use of much lower doses, by orders of magnitude (see also Section 3.3. below).

The marked adsorptive properties of remedy source and silica NPs (130-132) and nanobubbles formed during succussion in ethanolic solutions (78) contribute to NP formation and persistence from low to high homeopathic remedy potencies. That is, skeptics may be

correct that the bulk form materials are serially diluted out of solution past Avogadro's number; however, empirical evidence indicates that nanoforms of the source material and/or specific structural information remain (60, 61, 63, 113). The source NPs per se may be more reliably present in the lower potencies (61), i.e., less diluted potency forms. However, data show that some persistent source NPs and the remedy-modified silica nanostructures (or polymer NPs if made in non-glass vials (63)) are present across all potencies to convey and amplify remedy source-specific information (60,61).

At the same time, the data suggest the potential for greater variability of NP quantities and perhaps sizes and shapes at higher homeopathic potencies as currently manufactured. Data from a group studying the remedy *Gelsemium*'s properties suggest that NPs from plant remedies may be variable in surface qualities and biological properties as a function of manufacturing methods (63). On the other hand, homeopathic remedies are made from mineral, animal, and plant source materials. A different study observed some surface irregularities but not major size differences on electron microscopic imaging of different potencies of metal-derived remedies (61). Although certain specimen preparation methods in the latter study may have affected the totality of findings, this study nonetheless demonstrated remedy source-specific nanoparticles up to 200C.

For NPs, it is not only quantity, but also sizes, shapes, and other features of small particles that significantly change their biological effects (70, 83, 84, 133). *Increasing numbers of total succussions after serial dilution steps at higher homeopathic potencies would be equivalent to increased sonication time durations in modern nanotechnology* (116, 134). If so, then the properties of the resultant homeopathic source NPs should potentially differ nonlinearly at higher versus lower potencies of the "same" remedy, given likely smaller NP sizes and reduced aggregation after succussion. One study in animals did find more prolonged duration of effects at 200C versus 30C potencies of four different homeopathic remedies (135). Moreover, consistent with available data on size- and shape-dependency of NP effects (84), consecutively or successively higher potencies exert nonlinear and even sinusoidal oscillatory effects on bacterial cells, plants, and animals (9, 136-138). Catalytic effects of NPs can fluctuate up and down sinusoidally as a function of progressively increasing nanocrystal aggregate size (84). Recency of succussions may play a role by dispersing particles into smaller sizes (82, 133, 139) and thus altering the nature of physico-chemical and biological findings in homeopathic studies (121). Adding more trituration grinding steps in lactose for dry potencies or adding succussion steps after each dilution step in liquid potencies would serve to disperse any larger, aggregated nanostructures and thus potentially change their properties (73, 116).

Testable hypotheses for why the remedy source NPs persist at high potencies with bulk source molecules removed by dilution include NP adsorption onto inner surfaces of containers and other glassware (silica or polyethylene or other polymer tubes) used in preparation (60) and vial-to-vial transfer (61), as well as to silica crystals or polyethylene nanocontaminants shown to be present in solutions made in glass or synthetic polymers (60, 63, 64). Like other types of NPs (84), silica nanoparticles are highly reactive and adsorptive (140), with the capacity for augmenting immune responses to antigens and triggering systemic biological signaling by themselves (65-68, 87, 141-144). Some homeopathic clinicians, including Hahnemann in his later writings (71), prefer that patients self-administer remedies in water after additional succussions of their treatment bottle, rather than simply dissolving dry pellets (previously sprayed with remedy and dried) under the tongue.

The hypothesis related to this clinical observation is that the additional succussions will release more nanosilica with its non-specific immune-stimulating adjuvant effects and disperse remedy source material nanoparticles into smaller sizes that may have aggregated from Ostwald ripening during shelf storage or light exposure (133, 139, 145-149). Ostwald ripening is a spontaneous thermodynamic process in sol solutions, whereby nanoparticles redeposit onto larger particles in solution, thereby changing the physico-chemical properties of the material. The silica NPs would serve as an additional but not always essential vehicle, as well as a potential non-specific amplifier of remedy source NPs biological effects and their informational properties in liquid potencies prepared in glass (60, 64, 113). Table 3 indicates proposed nano-forms and their hypothesized roles in the effects of homeopathic remedies interacting with the living organism.

3.3. Clinical characteristics of nanoparticles

The significance of finding nanoparticles in homeopathic remedies is that NPs have very different properties from those of their respective bulk form materials, as a function of their small size (83, 84). NPs are not merely small versions of their respective bulk forms. Such unique properties can help account for various findings on homeopathic remedies (59, 112, 121). Nanosizing by mechanical milling of drugs leads to (a) greater bioavailability with improved absorption from oral, gastrointestinal, nasal, or dermal administration; (b) higher adsorptive capacity to attach other nanomaterials onto their surfaces and serve as drug, vaccine, or gene delivery vehicles for self-assembled agents; and (c) enhanced catalytic ability for chemical and biochemical reactions (83, 91, 111, 150-152).

Nanovaccines can elicit immunological responses in a single adjuvant dose for antigen quantities 1,000-fold lower, e.g., 2.5 nanograms, compared with amounts in ordinary vaccines of the same antigen (89). "Dose-sparing," i.e., ability to use lower doses, is a general feature of nanomedicines (90, 91, 153), as well as reduced side effect risks and better intracellular access (91). Silica NPs are particularly effective in an immune-boosting adjuvant role (142, 143).

The NP vaccine delivery vehicle adjuvants boost the danger signal quality of the intervention for the organism (90, 142-144, 154-156). As a result, the organism mounts an even more vigorous immune response than usual to minute amounts of antigen or other foreign material (68, 89). The body then sees the tiny quantity of antigen as an exaggerated external threat requiring a vigorous compensatory immune response. On the other hand, if a nanoparticle is toxic, the quantities that can still exert adverse environmental effects on living systems are also extremely low, e.g., 1 nanomolar concentration of nanoceria NPs (nano-Ce-O(2)) (94).

NPs cross membranes, including blood-brain barrier (157, 158), without difficulty, and travel, mainly via lymph but also blood, throughout the organism (83). Nanoforms of drugs, herbs, nutriceuticals, and vaccines can all dramatically reduce by orders of magnitude the dose of the agent needed to produce a given biological effect (76, 77, 88, 96, 159-161). Moreover, because of their large surface area to volume ratio, NPs are more atom-like in behavior, acquiring the different electrical, magnetic, thermal, optical, chemical, biological, and quantum effects compared with their bulk forms (84, 162). Electrons are located closer to the surface of NPs (84). Bacterial DNA nanoparticulates prepared with dilution and succussion show ability to transmit measurable electromagnetic signals (163). Gold, which is non-magnetic in bulk form, becomes magnetic in nanoparticle form (84, 162). Some NPs, like certain forms of silica, exhibit quantum macro-entanglement effects (118).

The properties of NPs are nonlinear in nature (98, 164). For instance, increasing amounts of sonication time (a modern method for creating intense turbulence in a solution, cf., succussion (63)), produce nonlinear changes in thermal conductivity properties of a carbon nanostructure (116). Low doses of a carbon nanocrystalline material can protect healthy cells while inducing anticancer effects via autophagy in human and rat glioma cells (98); the biomechanisms for high doses of the same nanomaterial differ. A study of the homeopathic plant derived remedy *Ruta graveolens* 6C with Calcium Phosphate 3X potencies reported similar findings in human glioma cells (45). Notably, modern nanotechnologists use calcium phosphate nanoparticles as effective drug and gene delivery vehicles (151, 165).

Nanoparticles also induce systemic immune responses, based at least in part on their ability to mobilize components of the reticuloendothelial network (68). Moreover, not only bacteria and viruses (166-169), but also silica nanoparticles and other non-viral NPs can also activate intracellular inflammasomes (142, 170). Inflammasomes are a protein complex considered to serve as danger sensors for environmental threats to the cell's survival (171-173).

Once activated, inflammasomes release pro-inflammatory cytokines such as interleukin-1 beta (174). In turn, cytokines modulate immune and inflammatory responses (156) as well as brain function and behavior (175, 176). Overall, NPs, infectious agents (e.g., viruses, which are also often nanosized) (83), and many other types of exogenous stressors (biological, chemical, physical, or psychological) can set into motion the multiple defense pathways in the cellular stress response network (68, 142, 170, 177-180). Similarly, homeopathic remedies can modulate cytokine release and immune function *in vitro* (47, 58), in addition to activating different patterns of heat shock proteins (52-54), one of the key sets of endogenous proteins in the stress response network of the body (179-183).

If homeopathic remedies are nanoparticles and nanocrystals of source material, how would they exert therapeutic effects? Are NPs not often toxic for cells and organisms? Even if homeopathic NPs are benign, how could such small quantities in the low doses used in homeopathic remedies initiate such large, organism-wide changes? The remedy source also has no relationship to the original causes of the patient's disease. How could an unrelated homeopathic agent trigger reversal of the adverse effects of an accumulation of prior stressors? The answers lie not in conventional pharmacology, but rather, in the body of empirical research on the biological stress response (52, 53, 69, 184, 185), physiological adaptation (186-193), cross-adaptation (194, 195) and cross-sensitization (196-201), as well as in complex adaptive systems science (10, 22, 35, 59, 189, 202, 203).

4. HORMESIS AND ADAPTATION: HOMEOPATHIC REMEDIES AS EXOGENOUS LOW INTENSITY STRESSORS

Both nanoparticles (69) and homeopathic remedies (52-54) can initiate hormesis. Hormesis is a term from pharmacology-toxicology and physiology that refers to universal biological adaptive processes of living organisms in response to low levels of an environmental stressor or toxin (69, 186, 193, 204, 205). In hormesis, the dose-response curve is nonlinear, typically biphasic, with low doses serving as stimulatory and higher doses serving as inhibitory for function. The beneficial adaptive responses of hormesis have been demonstrated in more than 8,000 scientific studies for agents ranging from low level radiation to chemotherapy drugs to environmental toxins to physical or psychological stressors per se (193, 206). The hormetic dose-response range in which such phenomena are observed falls into the nontoxic range, below the cut-off for the no-observed-adverse-effect-level (NOAEL) (193, 204). Hormesis mobilizes cellular defenses of the stress response system (54, 187, 188). Various investigators have concluded that the low doses stimulate the organism to recover from past effects of or to prepare itself for a future assault by the same or a cross-adapted, higher intensity stressor that would threaten survival (69, 187, 188, 190, 191, 207-211). Several have suggested that episodic low level hormetic stressors over a lifetime could promote longevity via enhanced systemic resilience (187, 190, 191).

If nanoparticles are highly bioavailable, active, and reactive and require much lower doses to produce

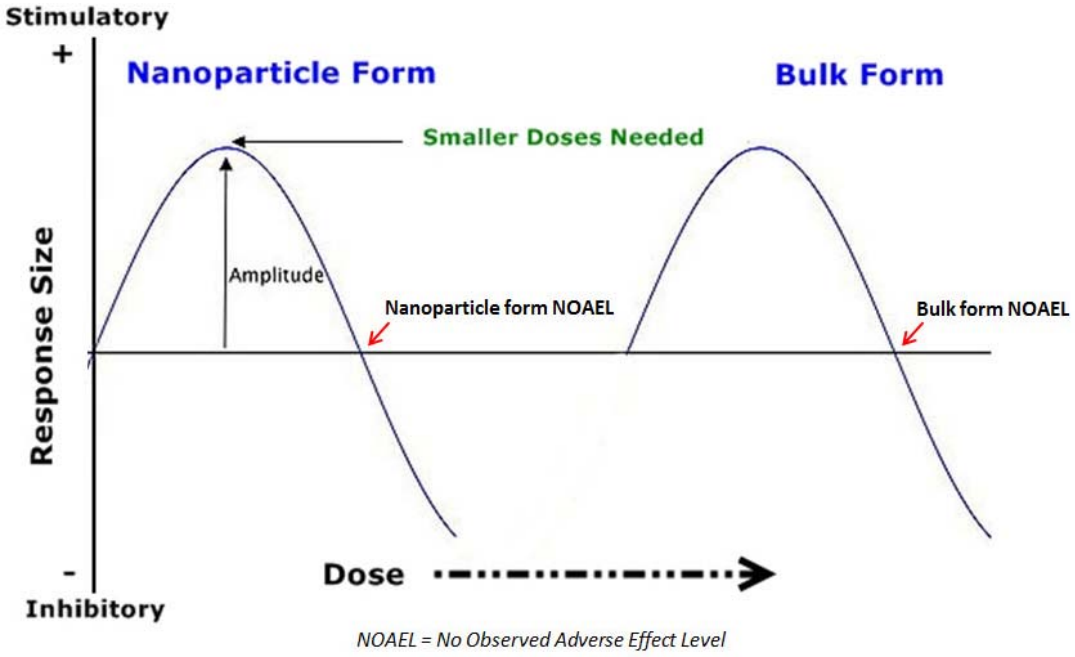

Figure 2. Nanoparticle forms have lower dose ranges for inhibitory and stimulatory responses compared with bulk forms. Nanoparticle forms require markedly lower doses to produce similar biological effects compared with bulk forms of the same material. This would also reduce the NOAEL (no-observed-adverse-effect-level) dose cut-off point for the beginning of the hormetic low dose range. Stimulatory responses would represent beneficial adaptive changes in the cell and/or organism in response to a given low dose (hormesis).

pharmacological or toxic effects than their bulk forms (70, 77, 89), then the doses of NPs that fall into the beneficial hormetic dose range, i.e., below the NOAEL, would of necessity have to be extremely low (69, 70). Figure 2 illustrates the lowering of the NOAEL dose cut-off for hormesis with nanoparticle forms versus bulk forms of a given material. This point translates into the scientific plausibility of exceedingly small amounts of homeopathic remedy nanoparticles being able to exert biological effects in a cell or organism (9). Homeopathic NPs, which are typically delivered in a pulsed or intermittent dosing regimen, would act not by direct pharmacological effects on receptors, but rather, as by inducing self-propagating adaptive responses in the organism to the remedy dose as an exogenous stressor or danger signal (68, 185). Khuda-Bukhsh *et al* have demonstrated the ability of homeopathic remedies to modulate biological signaling (40).

The organism then amplifies and self-organizes its responses with the passage of time (32, 35, 59, 184, 197, 203, 212-218). For example, Chikramane *et al* found a range of very low quantities of the homeopathic source material nanoparticles at the higher 30C and 200C potencies, e.g., approximately 10 to 4,000 picograms/milliliter (where 1 picogram per milliliter = 0.001 nanograms per milliliter)(61). The 6C potencies contained concentrations ranging from roughly 75 picograms/ml to 1300 picograms/ml. Consistent with the primary role of homeopathic nanoparticles as very low dose adaptive danger signals to the organism, even repeated olfactory administration of single homeopathic remedies at both lower and higher potencies in placebo-controlled studies on human subjects initiates progressive amplification and/or oscillation of quantitative electroencephalographic responses over time (27, 28, 30-32).

Variability in the comparatively crude manual grinding methods for traditional manufacturing of homeopathic top-down nanoparticles could certainly contribute to the variability from study to study and patient to patient in the effects of a given dose of remedy (5, 56, 74). Differences in the sizes and shapes, as well as the quantities, of source nanoparticles modify the nature and direction of their effects (84, 113, 116). It is also uncertain if or how the known quantum effects of nanoparticles (70, 84, 118, 123) might come into play in affecting biological function. Evidence with quantum dot types of nanoparticles indicates that very low dose nanomolar to picomolar concentrations exert long-lasting effects in living systems (70). However, these points do not support complete rejection of homeopathy as an implausible whole system of CAM.

Rather, understanding that homeopathic remedies are made in ways that can generate variable amounts of different sized and shaped source nanoparticles should steer scientists to explore modern nanotechnology methods for improving their production and nanomedicine uses (45, 72, 74, 101, 102, 113). Thoughtful examination of current procedures could lead to new developments for homeopathy on how to enhance remedy manufacturing

standards and testing procedures (132, 219-220). Nonetheless, even with potential limitations of its traditional manufacturing methods, the therapeutic potential and safety of homeopathy remain well documented in the literature (5, 6, 221, 222).

In the case of NPs, the quantities needed to activate the endogenous processes of beneficial adaptation of hormesis are extremely low (9, 69). Within homeopathy, Hahnemann focused on the adaptive reaction of the organism to the remedy as the origin of the therapeutic effects. He actually used low doses to minimize or avoid the initial direct actions of medicines on the organism, i.e., the toxic effects of conventional drug doses. Instead, he pointed out the importance of using low doses of medicines to evoke the adaptive reactions that throw off the pre-existing disease processes in the organism from within (71): *"…This back-action belongs to our sustentive power of life and is an automatic function of it, called the after-action or counter-action."*

5. HOMEOPATHY AS ADAPTIVE NETWORK NANOMEDICINE

Hormetic adaptations engage the biological plasticity and metaplasticity of the organism as a complex living system. In modern scientific terminology, the counter-actions that Hahnemann described are considered adaptive responses of the organism as a complex adaptive system or network (69, 184, 218, 223-227). Any medicine constitutes a perturbation of the biological steady state internal milieu of the organism, though high doses produce such strong direct actions that the adaptive reactions are masked until the drug is withdrawn. In contrast, for homeopathy, the low doses of the individually-salient nanomedicine, given intermittently, primarily reveal the organism's robust counter-action after only a minor or undetectable direct action. Conventional pharmacology relies on direct drug actions; homeopathic treatment relies on indirect organism reactions or adaptations (71).

The current research literature recognizes that the biology of the stress response in adaptation involves a multi-factorial set of interactive and self-regulatory pathways in the immune, endocrine, central nervous, autonomic nervous, and metabolic systems of the body (8, 40, 177, 181, 184, 215, 216, 218). Mobilizing one element of these stress response pathways typically cascades into activation of others throughout the rest of the interconnected network (68, 96, 179, 180, 184, 216-218, 228, 229). In an intact organism, the brain plays a hub role in coordinating and regulating the bidirectional information flow to and from the other components of the stress response network (216, 230). The stress response network is the organism's interface with or first responder to environmental change, threat, or danger (8, 68, 89, 171, 197). Furthermore, this adaptive network is an amplifier of endogenous reactivity to the same or a subsequent cross-sensitized threat (194, 195, 197, 198, 231, 232).

McEwen (215), Csermely (181), and others have postulated that many chronic diseases of developed societies reflect a cumulative overload on the adaptive capacity of the individual. As a result, genetic vulnerabilities interact with epigenetic influences, i.e., environmental stressors of all types at higher intensity, to induce dysfunctional shifts in physiological setpoints for protecting the cells and organism from adverse effects of stress. Thus, chronic diseases reflect cumulative maladaptation to what McEwen terms "allostatic overload" at the organism level (215) or Csermely calls "chaperone [protein] overload" at the cellular level (181) of network organizational scale.

In one-cell model systems, mobilizing heat shock proteins in the stress response network causes a self-reorganization of functional links between molecular effectors (179, 180). The adaptive changes in network linkages prepare the system biologically for better resisting or recovering from the environmental threat that the stressor represents (179, 180). Recovering from the effects of the stressor translates into restoration of the unstressed network configuration and interactional patterns (233, 234). Figure 3 illustrates the different types of functional network self re-organization that cells undertake in response to different levels of stress. Such processes also appear to have parallels in the nature of integrative healing from acute or chronic disease at the organism level of scale (202, 203, 212, 235). Complex network systems exhibit recurrent, interactive themes or motifs between global and local levels of scale (236). Given the essential contribution of the complex system to remedy effects, the model suggests that homeopathic NPs will only reveal their fullest capacity to trigger adaptive changes when evaluated in an intact organism rather than just a cell. In fact, Baumgartner, in reviewing the basic science research literature on homeopathic remedies, concluded that the most robust effects of homeopathic remedies appear to occur in whole organisms rather than isolated cell systems (112).

Thus, homeopathic nanoparticles are potent, salient environmental stressors for cells and the global organism as complex adaptive systems or networks. The endogenous adaptive response of the organism is strong enough in many cases to boost systemic recovery processes and overcome the established acute or chronic disease by reversing the complex set of adaptations originally made in response to past cumulative stressors of all types. Data show that endogenous adaptive responses can and do grow in magnitude with the passage of time (197, 237). The pulsed timing or intermittent dosing regimen of homeopathic remedies allows the organism sufficient time to react to a given discrete dose and to evolve its most complete self-amplified response.

The intensity of the reaction to a salient remedy stems from the enhanced adjuvant and stressor qualities of the nanoparticles in the remedy (69). The ability of the remedy to address the net adaptive dysfunctions of the whole system derives from cross-adaptation (194, 195, 232). That is, the adaptive responses that the remedy's source material can elicit are specifically cross-adapted (238) to the individual's unique pattern of previously established adaptations made in response to past higher intensity stressors (59, 215, 239, 240).

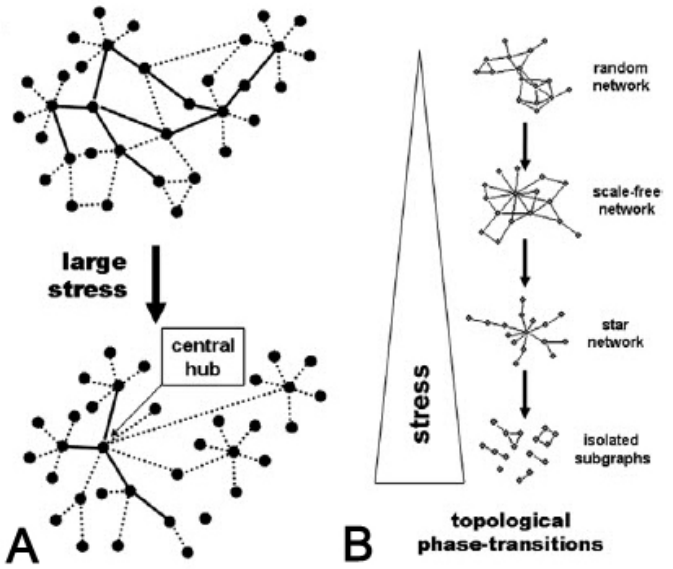

Figure 3. Network rearrangements in stress. The salient homeopathic remedy nanoparticles would serve as a hormetic low level biological stressor to disrupt disease-sustaining functional dynamics and network organization that had previously developed in the cell and/or organism during larger stress. The remedy-initiated disruption would permit the cell and/or organism as a complex adaptive system to self-reorganize in a healthier way over time during treatment. (a) Stress-induced decrease in the strength and number of links leads to detached elements, and results in an increased competition between the strongest hubs and bridges for remaining links. Parallel with this, an increased de-coupling (in extreme case: quarantining) of network modules is observed, which leads to simpler, less regulated, more specialized cellular functions. Solid and dotted lines represent strong and weak (high and low affinity) links, respectively. (b) In chronic stress or extreme changes in the environment parts of cellular network may undergo a topological phase transition, where the distribution of the number of neighbours becomes more and more uneven. Here the topology changes from a random network to a hub-containing network, where the number of neighbours has a scale-free distribution, then a star-network develops, where a 'dictator-hub' attains most connections, and finally the network falls apart to densely-connected small groups – called isolated subgraphs. Reproduced with permission from reference (180).

The scientific precedent for this type of cross-adaptation is found in an extensive research literature in physiology and neuroscience (194, 195, 197, 232). Stressors from different categories can cross-adapt or cross-sensitize with one another, e.g., hypoxia and cold temperature (195, 232), stress and amphetamine or cocaine (196, 241), formaldehyde and cocaine (199), sucrose and amphetamine or cocaine or ethanol (200, 242-245). Early life stress leads to persistent pro-inflammatory changes in modulation of immune function and increases susceptibility to multiple different diseases in adulthood (215, 239, 240, 246). Even adaptations to a single environmental toxin exposure with a fungicide in previous generations can carry over transgenerationally by inherited epigenetic changes (cf., "miasms" in homeopathic terminology (247)). The resultant adverse epigenetic adaptations lead to alterations in the brain chemistry, function, and behavior in subsequent generations' responses to stress (248).

A remaining question is why would a homeopathic remedy trigger the organism to reverse course and recover from a disease? Here the answer is that directionality of responses in a complex adaptive system is flexible, dependent partly on the intensity of the stressor (9, 214) and partly on the state of organism (197, 202, 249-251). A system at its physiological limits is potentially susceptible to undergoing massive changes, with nonlinear dynamical shifts upon the arrival of a small salient stressor such as a low dose of homeopathic medicine NPs (202, 237). The impact would be an abrupt self-organized phase transition into a new and different dynamical pattern (202, 251).

Low intensity stressors initiate adaptations in the opposite direction to those of higher intensity stressors (214). Adaptive plasticity is itself modulated by the phenomenon of metaplasticity in the organism, e.g., the plasticity of synaptic plasticity in the central nervous system (252). That is, the last stressor or stimulus potentially preconditions or primes the system to respond back in the opposite direction on the subsequent encounter with the same or cross-adapted/cross-sensitized stressor or stimulus (252). Thus, if prior higher intensity life stressors, infections, traumas, and adverse biological events have accumulated a stressor overload on the adaptive capacity of the organism (215), then the small intensity stressor of salient nanoparticles in a homeopathic remedy could trigger a sudden reversal in direction back towards health (202).

Metaplasticity reflects the effort of the organism to maintain function within a physiologically viable range around a set point as compatible as possible with good function and survival (218, 252). When adaptations to previous stressors have pushed function too far from the

healthy set point in one direction, the arrival of the next relevant stimulus can trigger adaptive changes that push function back in the opposite direction. The homeopathic remedy, with its salience to the emergent global themes or motifs of the organism (236, 253) in adapting to the established acute infection, injury, or chronic disease state (e.g., homeopathic modalities of worse at altitude or in cold temperatures, better at a certain time of day or after eating) would activate the organism's existing metaplastic priming to reverse direction and shift the set point and physiological range back toward a healthy normal.

As a precedent, prior treatment with a given stressor or drug in animals or people can elicit a change in the opposite direction for responses to the same or cross-adapted/cross-sensitized agent when the system is close to its physiological limits (213, 214, 237). A properly timed discrete pulse can also interrupt a cardiac arrhythmia or seizure in the brain, causing the system to revert to normal dynamical function (254-256).

Biphasic or oscillatory dynamics are a well-known phenomenon to researchers in nonlinear dynamical systems and complex systems science, especially at phase transitions from one steady state into another (202, 249, 250, 257). Empirically, homeopathic remedies can induce biphasic oscillatory responses in human subjects and animals in central nervous system and other psychophysiological outcomes that placebos do not cause, even when the remedy is not acting therapeutically (22, 27, 35, 48).

On the other hand, if clinical recovery occurs, homeopathic practice theory postulates that symptoms will reorganize over time to affect different bodily subsystems in a hierarchical manner. The correct remedy serves as an inducer of a qualitative phase transition in the overall organism (202, 212, 250). That is, during successful homeopathic treatment, changes shift spatially over time after the remedy dose, down the body, from inner organs outward toward the skin, and in reverse order of original appearance in time (235). The self-organizing properties of complex adaptive systems (180, 254, 258) would account for the latter observations under clinically effective homeopathic treatment.

6. SUMMARY AND CONCLUSIONS

The Nanoparticle-Cross-Adaptation-Sensitization model for homeopathic remedies (59) provides an evidence-based foundation for a comprehensive research program and new clinical approaches to integrative medical treatment. The perspectives of this paper and the data that will emerge from such a research program can help practitioners better understand when and how to utilize homeopathic remedies for their patients. For instance, the strong real-world track record of homeopathy in treating a range of infectious diseases (8, 222, 259-262) may be explained by the ability of salient remedy along with silica nanoparticles, to act as super-adjuvants, stimulate a vigorous increased immune response, and overcome the infectious agent (68, 89, 90).

The model also helps account for the importance of administering remedies only in a pulsed, intermittent manner until symptoms begin to change (263). At that point, it is the organism, not the remedy, that is carrying the response forward. Consequently, it is essential to stop giving additional remedy doses unless and until symptoms begin to plateau or relapse (263). The risk of excessive dose frequency in homeopathy would be inducing worsened symptoms, as is found in homeopathic remedy pathogenetic testing on initially healthy human subjects or animals (48, 264, 265).

Homeopathic remedies, because of the way they are made by intensive manual grinding in lactose (72, 101, 102, 106) and/or vigorous shaking to create turbulence in ethanol-water solutions (74), are small quantities of nanoparticles of their source material (60, 61, 63). Remedies stored in glass and delivered after additional succussions in water could also contribute nanosilica NPs as immune adjuvants and conveyors of remedy source-specific structural information. Succussions could also disperse source nanostructure aggregrates into smaller sizes at the moment of administration. Consistent with remedy NP aggregation, Elia *et al* (121) previously showed that shelf storage of liquid remedies in small volumes leads to measurable changes in thermal and electrical conductivity properties. Such findings could relate to changes in NP morphology from Ostwald ripening during storage. Nanoparticles are highly adsorptive, active and reactive agents with properties that differ markedly from those of their bulk forms (83, 84). Used homeopathically in very low, intermittent doses within the hormetic dose-response range, remedies trigger adaptive, self-amplified reactions in the local cells (52-54) and global organism (28, 30, 59).

Because of the interconnected network nature of complex living systems (202, 224, 225), the changes that a small dose of remedy nanoparticles can initiate in one component of the stress response network, lead to a large, systemic cascade of adaptive changes. The homeopathically-induced adaptations constitute a nonlinear phase transition of system setpoints and dynamics of the organism into a qualitatively different, healthier state. The remedy source's salience to the pre-existing adaptations that the organism with disease currently experiences is the basis for large magnitude salutary changes throughout the organism as an integrative whole system (cusp catastrophe (202) or self-organized criticality (251) events in complexity science terminology). Global and local levels of organization within the organism share interactive themes or motifs to which the salient remedy effects are well-matched (247, 253, 263, 266-268). Once initiated, changes at global and local levels of the system shape each other's dynamics back towards recovery and better health (18, 59, 212).

Based on the evidence, trying to invoke direct linear, local interactions of ordinary drug ligands with specific receptors that characterize conventional pharmacological effects is insufficient to explain the data on homeopathic remedies. Unlike conventional biomedical drugs, homeopathic remedies are chosen to be specific to

the emergent themes of dysfunction in the entire organism, not necessarily to the mechanism of only one specific local symptom (263, 269). Placebo effects are also inadequate to explain the totality of the data (5, 6). A large number of placebo controlled plant, animal, and cellular studies, as well as preclinical and clinical studies on human subjects, indicate that remedies exert effects distinct from placebo (5, 8, 270-273).

Homeopathy is not a conventional pharmaceutical practice; remedies are not conventional drugs. Rather, as nanoparticles, homeopathic remedies are low intensity environmental stressors that the organism detects as threats to its survival. The biology of the stress response networks mobilizes to address the remedy-specific challenge. The nanoparticles in the remedy, augmented by silica nanostructures, also act as adjuvants and/or non-immunological stressors to provoke a disproportionately strong systemic reaction. Immune, inflammatory, metabolic, endocrine, and nervous system pathways (8, 68, 170, 180, 184, 193, 216, 218, 230, 233, 274) are likely involved in carrying out the adaptive changes in response to an individually salient remedy. Quantum properties of nanoparticles (84, 118, 123) may also contribute to some findings with homeopathic remedies (124).

The political biases against homeopathy remain intense. Biases fuel skepticism even when scientific evidence shows the skeptics' assumptions and beliefs to be incorrect in their total rejection of the plausibility of homeopathy. If anything, this CAM/IM field was centuries ahead of its time, and modern science is finally providing measurement tools such as atomic force and transmission electron microscopy (60, 61, 84), specialized forms of spectroscopy (63, 78) and nanoparticle sizing techniques (219), multivariate biological stress response profiling (177), systems biology (275, 276) and nonlinear dynamical analytic methods for physiology and behavior (18, 35, 202, 203, 257, 277) to test and refine the model. However, in view of the unrelenting skepticism that homeopathy has faced since its inception, we propose that future research on "homeopathic remedies" and the practice theory of "homeopathy" instead begin using new terminology.

Taken together, the evidence indicates that a modern, scientifically more relevant, but neutral integrative term for homeopathy should be "adaptive network nanomedicine."

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