

Exploring Possible Mechanisms of Hormesis and Homeopathy in the Light of Nanopharmacology and Ultra-High Dilutions

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Abstract

Serially diluted succussed solutions of a suitable drug/toxic substance can exhibit physicochemical and biological properties even far beyond Avogadro's limit defying conventional wisdom. They can show hormesis, and homeopathy uses them as medicines. Many studies confirm that they can have an impact on gene expression different than controls. Water in the exclusion zone phase can have memory but for a short period. However, the nanoparticle as the physical substrate can hold information. Nanoparticle and exclusion zone duo as nanoparticle-exclusion zone shell can provide a prolonged memory. The Nanoparticle-Exclusion Zone Shell Model may be an important step toward explaining the nature and bioactivity of serially diluted succussed solutions used as homeopathic medicines. This model may also provide insight into the workings of hormesis. Hormesis is the primary phenomenon through which homeopathic phenomenon may have evolved exhibiting the principle of similars. Hahnemann exploited it to establish homeopathy. The nanoparticle-exclusion zone shells present in the remedy, selected on the principle of similars, can be patient-specific nanoparticles in a symptom syndrome-specific manner. They can carry the drug-specific information for safer clinical applications in an amplified form for high yielding. It suggests homeopathy is a type of nanopharmacology.

Keywords

hormesis, homeopathy, homeopathic medicine, principle of similars, nanomedicine, nanopharmacology, exclusion zone, the nanoparticle-exclusion zone shell model

Introduction

During 1880s, a German pharmacologist Hugo Schultz observed a biphasic dose response characterized by a low dose stimulation and a high dose inhibition.^{1,2} Calabrese states it more accurately as, "It is a dose-time-response relationship in which there is an initial dose-dependent toxicity response followed by a compensatory/rebound response, such that at low doses the response becomes greater than the original background state or control group value."³ This initial dose dependent toxicity response is frequently observed in homeopathy too as an initial aggravation of symptoms of the patient.

Schultz claimed that the phenomenon of biphasic dose response explained the principle of homeopathy. This assertion led to his important discovery's marginalization,⁴ as a schism had developed in medicine after the advent of homeopathy. Calabrese and colleagues noted the problem.⁵ They distanced hormesis from homeopathy in an effort to establish hormesis well in modern science.⁶ However, in 2010, Calabrese along

with Jonas started a debate on possible links between these 2 systems.⁷

In studying hormesis, the dose is conventionally kept just below the toxic threshold, while in homeopathic practice it is usually lower than this and can even be beyond the physical existence of the original agent if prepared in a typical way. When using plant substances and liquids, Hahnemann diluted the solution with water or a mixture of alcohol and water. He used centesimal (1:99) scale for standardization. After each

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dilution, he vigorously shaken (he used the term “succuss” which is a type of more forceful shaking) the mixture at least 40 times. When he used mineral agents and various chemicals that were insoluble in water/alcohol, he diluted them with lactose (milk sugar) and triturated (i.e., grinded) the mixture. He termed this pharmaceutical process of dilution and succussion (or trituration) as “potentization” because he and his fellow homeopaths found that the greater number of potentizations led to longer and deeper effects of the drugs and the need for reduced repetition of them. But once a medicinal agent is diluted in the ratio of 1:99 12 times (i.e., in its 12C potency) or in the ratio of 1:9 24 times (i.e., in its 24X potency), according to Avogadro’s number, there would be in high probability no remaining molecules of the original medicinal agent (i.e., source-drug) in the solution. In homeopathic practice, far higher dilutions than this are used regularly in daily practice. Discussion on how these effects can happen will be discussed later.

Hormesis and homeopathy are interrelated in many ways. The robust research methodology developed in hormesis can help in carrying out research work in homeopathy.⁸ Toxic substances that do not exhibit hormesis can do so after their potentization, at least those with which life evolved.⁹ Medicinal effects of serially diluted succussed solutions are not confined to substances conventionally used in homeopathy as source-drugs. Chemicals like histamine,¹⁰ thyroxine,¹¹ and aspirin¹² diluted homeopathically, even far beyond Avogadro’s limit, have found biological models showing opposite effects to those from their pharmacological doses.⁹ Similarly diluted sodium butyrate, a promising therapeutic agent for cancer treatment which targets epigenetic pathways, found modulating the transcriptome of HEK 293 cells.¹³ Also, the taxane anti-cancer drugs paclitaxel and docetaxel, used in chemotherapy, diluted similarly showed differential effects on the genes of breast cancer cells without being cytotoxic.¹⁴

Many different research groups have shown that various chemicals/drugs diluted homeopathically even beyond Avogadro’s limit can stimulate hormetic responses in living cells.¹⁵⁻¹⁹ Commenting on the work of Chikramane et al,²⁰ Calabrese suggested it as a step forward toward unification of hormesis and homeopathy.²¹ In fact, the early treatments of Hahnemann can now be identified as hormetic in nature.⁹ In the beginning, he diluted his drugs simply up to the level that ended their toxicity, and indications to administer them according to the principle of similars were not known enough except the toxicity they cause.

Nanoparticles can cause a hormetic dose-response.²² In succussed ultrahigh dilutions of drugs/toxic substances used in homeopathy as medicines, such nanoparticles are present.²³⁻²⁷

Evidence confirms that hormesis is a generalized adaptive response that may be further generalized to nanoscale xenobiotic challenges.²⁸ A particle less than a 100 nanometer in size is called a nanoscale particle or nanoparticle. Due to its large surface area in comparison to volume, its properties can be extraordinary in comparison to its bulk form. It can even act as an environmental sensor.²⁹ Along with interfacial water on

their surface, they, as nanoparticle—exclusion zone shells, can retain the information specific to the source-drugs/toxic substances.³⁰ Thus, such ultra-high dilutions can be bioactive defying conventional wisdom.

There have been 2 significant objections against homeopathy. First, its medicines are often ultra-high dilutions of drug-substances that can hardly contain any remaining molecules. Secondly, it performs ambiguously in double-blind type clinical trials.

Large reviews of such research have found evidence of benefit from homeopathic medicines,³¹⁻³⁴ while other reviews haven’t.^{35,36} These ambiguous results stem from the fact that these trials are designed to test modern medicine while it is a highly individualistic therapy. Such trials are not even suitable to test a hormetic agent’s efficacy, as the toxic threshold varies from person to person.³⁷

Despite the objections and controversies against homeopathy, its popularity has been increasing worldwide. It has been practiced virtually in every country in the world for the past 200 years.³⁸ It has been widely used by medical doctors and numerous other health and medical professionals as a complement and as an alternative to conventional medical care to treat a wide variety of physical, emotional, and mental health complaints. It is also used in self-treatment by the general public for minor, self-limiting complaints. The World Health Organization considers homeopathy to be a part of “traditional medicine.”³⁸

How can ultra-high dilutions, as used in homeopathy, be therapeutically effective and also exhibit hormesis? Advent of nanoscience and new understanding about water can help to answer this question. The present paper explores this possibility along with the relationship between hormesis and homeopathy.

Emergence of Nanoscience

Richard Feynman was a legendary physicist who as early as 1959 helped herald in the revolution in nanotechnology and nanosciences.³⁹ The revolution emerging from nanosciences is still just beginning.

Diamond and graphite are both made of pure carbon, but a diamond is considered the hardest mineral in the world, while graphite is one of the softest. Likewise, gold is that shiny, golden noble metal that doesn’t tarnish, melts at 1,948 degrees (F), and is non-magnetic. And yet, in nanosizes as small as 10 nm, the gold particles absorb green light and thus appears red, its melting temperature decreases considerably, and gold is no longer noble but at 2-3 nm exhibits significant magnetic properties.⁴⁰ Moreover, recent research has observed that gold nanoparticles have an effect upon B-lymphocytes.⁴¹

The point to the above facts is that the properties and effects of an agent is not simply its chemistry as we know in bulk form, but also its size. In fact, specific agents in nanoscale amounts can have significant effects and even dramatically different effects than bulk amounts of the same agent. By acknowledging the scientific fact that gold at nanoscale becomes

magnetic, we begin to understand that nano sizes of a substance can drastically change its properties.

The United States' Government website well describes how and why nanoscale materials play a much larger role in material properties and interaction than normally assumed, "Nanoscale materials have far larger surface areas than similar masses of larger-scale materials. As surface area per mass of a material increases, a greater amount of the material can come into contact with surrounding materials, thus affecting reactivity."⁴² This website continues, "Nanotechnology is not simply working at ever smaller dimensions; rather, working at the nanoscale enables scientists to utilize the unique physical, chemical, mechanical, and optical properties of materials that naturally occur at that scale. Over millennia, nature has perfected the art of biology at the nanoscale. Many of the inner workings of cells naturally occur at the nanoscale. For example, hemoglobin, the protein that carries oxygen through the body, is 5.5 nanometers in diameter. A strand of DNA, one of the building blocks of human life, is only about 2 nanometers in diameter."⁴²

Neal Lane, former director of the US National Science Foundation (NSF) said, "If I were asked for an area of science and engineering that will most likely produce the breakthrough of tomorrow, I would point to nanoscale science and engineering."⁴³ A 1999 report from the NSF Technology Council predicted that nanotechnology's impact on the health, wealth, and security of the world's population is expected to be "at least as significant as the combined influences of antibiotics, the integrated circuit, and human-made polymers."⁴³

The Use and Importance of the Nanoscale in Nature

Before exploring the possible mechanism behind the working of serially diluted succussed solutions, it is interesting to see the importance of too small in Nature. In this regard, there is a famous quote from Johannes Kepler: "Nature uses as little as possible of anything."

Nature is replete with specific examples of the powerful impact that results from extremely small doses of specific substances to significantly change living things and to alter physiologies and behaviors. We all know that every living creature is hypersensitive to whatever it needs to survive.

It is widely known that dogs have a truly amazing sense of smell and can follow a human trail despite the fact that a person leaves only approximately 4 billionths of a gram of odorous sweat per step.⁴⁴ Sharks can detect small concentrations of blood in the water or even slight perturbations that humans create while swimming, despite the great amount of volume that our oceans hold. And then, of course, are the truly awesome sensitivity that various insects have to pheromones, which are sexually attracting hormones. Male night moths can find females on a dark moonless night, and if necessary, even against the wind. A male silkworm will fly many miles to find its female insects.⁴⁴

It is no simple coincidence that pheromones are sensed only by those in the same species who emit them (akin to the homeopathic principle of similars), as though they have developed exquisite and specific receptor sites for what they need to survive and to propagate their species.

Ultimately, we only need to look at the significant influence that various chemicals have in our own human body to be in awe of the remarkable influences that exceedingly small doses have:

- Interleukin-1 for T-cell clone proliferation: 2.5×10^{-19} mol/L (19X)*
- Platelet-activating factor for decrease of luteinizing hormone somatostatin: 10–17 mol/L (17X)
- β -endorphin to modulate natural killer cell activity: 10–18 mol/L (18X)
- Tumor necrosis factor for synergistic action with various drugs: 10–14 mol/L (14X)
- Leukotrienes for release of luteinizing hormone: 10–20 mol/L (20X)⁴⁵

* Refers to the homeopathic notation in terms of its decimal scale (1:9) dilution.

From Insignificance to Even Absence: Ultra-High Dilutions as Medicines

Samuel Hahnemann (1755-1843) was translating a medical treatise and got fascinated with the information that Cinchona (known as Peruvian bark) which cures malaria and which produces symptoms similar to it when taken in excessive doses.⁴⁶ Hahnemann came to realize that a drug cures a disease because it causes its similar symptoms. He then radically shifted his orthodox medical practice to one based on this principle of similars. He chose to dilute his drugs to reduce the adverse effects caused by them. He noted that such dilutions were more effective as medicines when he administered them to patients at their homes, where he used to go on a horse cart often through bumpy roads.^{30,46} He wondered if the vigorous turbulence of the liquid solutions increased the pharmacological actions of his medicines. For standardization of his medicine, he used a centesimal (1:99) dilution scale. The decimal (1:9) dilution scale was introduced later by Constantine Hering. Dilutions of 1:9 are annotated as "X" potencies, while dilutions of 1:99 are annotated as "C" potencies, following the standard for Roman numerals.

During the first 3 decades of developing homeopathy as a therapeutic system, Hahnemann and his fellow medical doctors utilized doses that were iterated for a small number of times. In 1829, Hahnemann expressed an urgent necessity to limit the number of dilutions that fellow homeopaths used in practice to the 30C potency.⁴⁶ In fact, when he had heard that some fellow homeopaths, including one who was also a respected Russian General, used homeopathic medicines that were diluted 1:99 over 1,000 times, Hahnemann wrote to these colleagues asserting, "I do not approve of your potentizing medicines higher

than [the 30th centesimal]—there must be an end to the thing.”⁴⁶ And yet, over time, Hahnemann himself tested these homeopathic medicines that were potentized over 1,000 times and was surprised and impressed to discover that these medicines worked and even required fewer repetitions of dosage than those medicines that underwent fewer iterations.

Despite Hahnemann’s initial skepticism of the extreme ultra-low doses of medicinal agents that his colleagues began to use, millions of practicing homeopaths and hundreds of millions of homeopathic patients have utilized these doses to seemingly effective therapeutic benefits. Both hormesis and homeopathy use various toxic substances below their pharmacological dose. Instead of primary pharmacological action of toxin/stressor, they utilize the body’s reaction to it, i.e. the secondary action of it for healing. The primary action of a toxic substance or medicine is its direct toxic effect; the secondary action is what the body does to heal itself from this agent.

However, while hormetic studies explore the effect of extremely small doses,⁴⁷ homeopathic applications and studies utilize even lower doses which are prepared in a typical way of potentization. How unusual is it for extremely small doses of a substance to have substantial biological and physiological effects? Homeopathic medicines are regularly sold in most of the countries including American health food stores and pharmacies. How these medicines can work is therefore worthy of study.

In this regard, new research reveals that homeopathy utilizes the organism’s reaction against (or secondary action of) toxin/stressor possibly via its specific information stored in nanoparticles and interfacial water on them as nanoparticle-exclusion zone shells.³⁰ Thus, the most common criticism that homeopathic doses are “too small” to contain any original medicinal agent to have any biological effect becomes irrelevant. Further, it is explained that homeopathic phenomenon is exclusively therapeutic and genetically deeper in action than hormesis, which is a basic and general phenomenon.⁹

Principle of Similars in Historical Perspective

Homeopaths claim that tiny doses of their medicines will only have benefits if and when the toxicology of the agent is “similar” to the symptoms that the sick person is experiencing. This pharmacological principle, called “the principle of similars,” forms the basis of this medical specialty, and it leads the practicing homeopath to determine which medicinal agent to prescribe. Thus, homeopathy is an adaptive stress-response therapy and therefore it is holistic in nature.⁹

Samuel Hahnemann discovered and developed the system of homeopathic medicine, but he was not the first physician or healer to refer to or utilize the “principle of similars” in healing. This pharmacological principle of using medicinal agents that cause the similar symptoms that the sick person is experiencing is an ancient principle about which Hippocrates (460 BC-370 BC) wrote,⁴⁸ Paracelsus (1493-1541) advocated in the 16th century,⁴⁸ and that has been used by various cultures since the distant past.⁴⁹ L.J. Boyd, a professor of medicine at the New

York Homeopathic Medical College (now called New York Medical College) wrote a highly referenced book in 1936 on the history of the “simile in medicine” where he chronicles in detail the various uses of this principle in healing throughout history and through various cultures. Of additional interest is the fact that he dedicated this book to the Board of Regents of the University of Michigan due to their support in creating a homeopathic medical school at that respected university.⁵⁰

Hippocrates was known to have referred to the use of similars as one school of thought and practice of his time, writing: “a disease develops by means of its like and is cured by means of the use of its like,” as well as “the fever causing the development of inflammation will be caused and cured by the same agent.”⁵¹ Even the ancient Oracle at Delphi proclaimed the value of the principle of similars by stating, “That which makes sick shall heal.”

The principle of similars that lies at the heart of homeopathy refers to a drug’s power to elicit a healing response when given in extremely small and specially prepared doses to people who exhibit symptoms similar to the medicine’s toxicology.⁵² Because symptoms are understood as defensive functions of the organism in its efforts to survive, there is a certain logic to the idea that the medicine that mimics these symptoms can and will help to heal this person. Ultimately, homeopathy is a type of “medical biomimicry,” that is, the use of a medicinal substance is chosen for its unique ability to mimic the symptoms the sick person is experiencing.

This principle of similars may be thought to be reminiscent of vaccination because this common medical practice utilizes small amounts of pathogens to stimulate an immune response to the disease the pathogen is known to create.⁵³ Although there are many differences between homeopathy and vaccines, Emil Adolph von Behring (1854-1917), the scientist who discovered the diphtheria and tetanus vaccines and who is canonized as the “father of modern immunology,” pointed directly to homeopathy as one of the inspirations to his discoveries that led him to win the first Nobel Prize in medicine in 1901.⁵⁴ After being granted this high honor, he finally felt secure enough to express his own appreciation for homeopathic medicine:

“In spite of all scientific speculations and experiments regarding smallpox vaccination, Jenner’s discovery remained an erratic blocking medicine, till the biochemically thinking Pasteur, devoid of all medical classroom knowledge, traced the origin of this therapeutic block to a principle which cannot better be characterized than by Hahnemann’s word: homeopathic. Indeed, what else causes the epidemiological immunity in sheep, vaccinated against anthrax than the influence previously exerted by a virus, similar in character to that of the fatal anthrax virus? And by what technical term could we more appropriately speak of this influence, exerted by a similar virus than by Hahnemann’s word “homeopathy”? . . . I am touching here upon a subject anathematized till very recently by medical penalty: but if I am to present these problems in historical illumination, dogmatic imprecations must not deter me . . . only the road of Homeopathy lead to my goal.”⁵⁵

If and when a person's syndrome of symptoms is adequately similar enough to the medicine's toxicology, the person has a special hypersensitivity to this medicinal agent. This phenomenon is well-known and regularly observed by people with allergies. A study published in the high impact *Journal of Allergy and Clinical Immunology* actually found more significant benefits from homeopathic doses of histamine and bee extracts (*Apis mellifica*) than specific sublingual immunotherapy in treating 74 children for intermittent and persistent allergic rhinitis.⁵⁶

This "like-affecting-like" phenomenon may be akin to an important observation in music whereby a "C note" will be hypersensitive or resonant with other "C notes," even at a distance. This principle of similars is also observed in electromagnetics: if a magnet loses its magnetic field, it can be recharged by strapping another magnet to it, with the north pole of one magnet near the north pole of the weakened magnet.

Ultimately, the homeopathic principle of similars is a systematic methodology to finding a medicine to which the person will be hypersensitive, even in tiny doses, and 200 years of experience by homeopaths finds that ingesting such a specific medicine will augment the immune and defense systems.⁵⁷⁻⁶⁰

How Ultra-High Dilutions May Work as Nanomedicines

Homeopathic dilution in iteration (i.e., potency) greater than 24X or 12C would in high probability have no remaining molecules of the source-drug. Any such solution, as conventional wisdom suggests, should not act as medicine. It really does act in such a manner. The scene entirely changes, if at each dilution level, such a solution was shaken violently. Then, it not only becomes bioactive but becomes more and more strong with such increasing serial dilutions.

"Memory of water" has been described as an explanation for this phenomenon^{61,62}; but when Benveniste and colleagues could not reproduce their results in front of the visiting *Nature* team,⁶³ it brought much controversy and even ridicule to homeopathy. Later, Elia and Niccoli reported that the procedure of dilutions and succussions is capable of modifying in a permanent way the physico-chemical features of water.⁶⁴ Recently Kokornaczyk et al have also found fundamental differences when evaluating evaporated water droplets from solutions of medicine that undergo the usual "succussion" as compared with light gentle mixing of liquids.⁶⁵

Malarczyk et al serially diluted formaldehyde at 1:100 ratios up to 20 iterations.¹⁹ They observed that living cells responded to these ultra-molecular dilutions providing a basis for a scientific explanation of hormesis and the therapeutic effect of homeopathic dilutions.

Ullman suggested that homeopathic medicine could belong to nanopharmacology.⁶⁶ Using probing tools of nanoscience, many independent research groups confirmed that nanoparticles are present in ultra-high dilutions used as medicines in homeopathy.^{23-27,67,68}

The vigorous shaking process used in homeopathy increases the water pressure in the glass bottle substantially. A lot of bubbles and nanobubbles are formed. Some researchers have claimed they play a possible role in the bioactivity of such dilutions.^{69,70} As particles moving against air get negatively charged, they would definitely help in the exclusion zone build-up. Thus, they can play an important role in preparing a homeopathic medicine, but they cannot be an integral part of the finished medicine.³⁰ Otherwise, homeopathic medicines would not have enjoyed an unlimited shelf-life even on sugar-globules soaked once with it. Their bioactivity does not decrease with aging if stored properly.

When these nanobubbles implode, they release heat and pressure that creates physical conditions that are different from normal water at rest.⁶⁹ This highly pressurized water then pushes the floating silica fragments into whatever medicinal agent is in solution, and due to the increased surface area that nanoparticles are known to have, the silicates can form a coat around the source nanoparticles.⁷¹ Then, when the homeopathic manufacturer seeks to raise the potency of the medicine by pouring out 99% of it, taking the remaining 1% as sticking to the glass walls as "seed," many of the silica fragments simply cling to the glass walls. It is no wonder that nanoparticles persist despite large numbers of serial dilutions (with succussions in-between each dilution). This can happen with the Korsakoff method of raising potencies using the same bottle again and again. However, in the Hahnemannian method, 1% of the medicine is poured out always in a new bottle, and 99% of the solvent is added; and then the whole solution is succussed to raise the higher potency of the medicine.

Chikramane et al studied 6 metal-based homeopathic medicines which were commercially made and purchased from the market and so controls were not available to compare the results. They found that nanoparticles of the source—drug metals were present in them nearly in the same concentration 6C potency onward.²³ As these medicines were commercially made and purchased from the market, controls were not available to compare the results. Still, they claimed that these nanoparticles could survive sequential dilutions after 6C potency. To explain it, they proposed the froth floatation hypothesis.⁷² According to this hypothesis, after succussions of the dilution, all the source-drug floats forming the uppermost layer which is 1 part of the whole and this 1 part as "seed" is poured out into 99 parts of solvent to raise the next potency.

Upadhyay explained that the froth floatation hypothesis of Chikramane et al⁷² is an inadequate explanation for how all homeopathic medicines may work.^{73,74} He gave several reasons like the source-drug of homeopathic medicine can be water/alcohol soluble, which cannot float as froth as possible with an insoluble drug. The source-drug can be even a non-material entity like X-ray, magnetic field etc. Moreover, dilution can also be carried out through trituration in dry form taking lactose as a diluent. Thus, if a source-drug is present in high potency homeopathic medicine, it can be due to contamination or impurity, as Avogadro's number is respected in the case of nanoparticles too. Thus, the presence of source-drug

in extremely low level as at nanoscale is very likely in commercially-made market-purchased medicines. Using self-made samples in laboratory, Van Wassenhoven et al could not validate the findings of Chikramane et al.⁷⁵

As Van Wassenhoven et al could not detect the source-drug even at 4C potency level, where such a presence is expected, this seems to question the sensitivity of the tools they used (Bellare, personal communication, March 2, 2021). Bellare notes that Van Wassenhoven, et al used dynamic light scattering, SEM with EDX, which are nano-analysis techniques that have limited capability to detect ultrahigh dilution samples. A TEM method is essential to detect the particles. Bellare complains, "The self-made medicines of Van Wassenhoven et al were prepared in water alone without using ethanol/water solutions, and this could have resulted in their not finding of any starting ingredient. The importance of ethanol in encapsulating and retaining the particles was demonstrated in Temgire et al."⁷¹ But homeopathic medicines are also prepared in water, and they work too. The purpose of study was not to look for the source-drug nanoparticles per se in them but for how they work.

Upadhyay and Nayak had also explored homeopathic medicines with nanoscience tools with self-made samples.²⁴ They observed the silicon-rich nanoparticles in them and suggested that the source-drug specific information they might have through epitaxy. They further suggested that these nanoparticles along with the exclusion zone water on their surface might carry this information "to the target in the 'size' increasing with dilution degree of the medicine."

Water as conventionally known with chemical formula H_2O virtually does not have memory. In presence of oxygen, under pressure, exclusion zone water ($H_3O_2^-$) builds up, particularly on a hydrophilic surface. Prigogine medal awardee Pollack calls it the fourth phase of water.⁷⁶ He and colleagues have studied it in detail for its extraordinary properties. It excludes nearly everything like dirt, dust and even solutes from it and so got the name. It forms honeycomb type hexagonal lattice and so can have "memory": "When reports of information storage in water surfaced in the late '80 s, world reaction was skeptical. This seemed impossible. Water molecules are known to jiggle around randomly at a furious pace; there seemed no possible substrate for long-term memory. That changed with the advent of EZ water. The structural lattice is essentially fixed. Oxygen and hydrogen atoms lodge at fixed positions within the lattice, and if any one of those atoms could get modified, that would constitute information. Modification possibilities abound: oxygen atoms have 5 possible oxidation states: -2 , -1 , 0 , $+1$, $+2$. Hence the potential for high-density information storage is extraordinary."⁷⁷

Water is a universal solvent and silica is ubiquitous. Solutes in it and leaching from glass walls form nanoparticles. During succussions, up to 6 ppm of silica fragments fall from the glass into the water.^{70,78} and pressure in the glass bottle increases substantially.⁶⁹ Further, oxygen in air mixes with water under extra pressure and this leads to the formation of EZ. But EZ erodes with time naturally by combining a hydronium ion (H_3O^+) with EZ structural unit (OH^-), resulting in 2 water

molecules.⁷⁶ However, EZ growth, by absorbing infrared energy from the environment balances the natural EZ erosion reaching a steady state.⁷⁶ Thus, it cannot retain information for a prolonged period. Upadhyay suggested that nanoparticle and exclusion zone together as nanoparticle-exclusion zone shell can retain substance-specific information for a prolonged period of time as its memory.³⁰

Homeopathic medicines are not only made in glass but also in porcelain to carry out trituration process for non-soluble drugs and occasionally in plastic too.⁷⁹ These different containers release nanoparticles from its constituent parts which can adsorb a medicinal agent due to their increased surface areas: be it glass that would release silicon quantum dots and silicates that can form silica nanoparticles or be it plastic that would release carbon quantum dots and larger carbon nanoparticles. Research on nanoparticles has confirmed substances placed in water solutions become embedded with the nanoparticle materials of the container.⁸⁰

Much is hidden in the lack of fundamental knowledge of the surface structure and surface energetics of the nanoparticle.⁸¹ Its increased surface area enables it to be highly reactive, capable of adsorbing other materials in solution onto the particle surface, thereby modifying the particle properties. Sometimes, these efforts are called doping of the nanoparticle.⁸² Recently, selenium—doped carbon quantum dots have been found efficiently ameliorating secondary spinal cord injury via scavenging reactive oxygen species.⁸³ A synthetic nanomaterial for virus recognition has been produced by surface imprinting using silica nanoparticle as a carrier.⁸⁴ Nanoparticles have been found to have enhanced bioavailability, electromagnetic, and quantum properties compared with bulk form.⁸⁵

Keeping in view the properties of nanoparticle and exclusion zone, Upadhyay³⁰ suggested "The Nanoparticle-Exclusion Shell Model" to explain the nature and bioactivity of a serially diluted succussed solution as: during the first 3 centesimal iterations, the drug/toxic substance modifies the structure of nanoparticles present in the solution. During the violent strokes, the drug can be adsorbed, doped or can make imprints on the nanoparticle. Thus, the nanoparticle acquires drug—specific information in "crude and condensed form," so does the exclusion zone builds up around it after the violent strokes. In the further iteration, one part of this solution is taken as "seed" and added to 99 parts of water and violent strokes are made. The exclusion zone shells get peeled off and spread in the whole solution. Then, new exclusion zone shells, containing a fraction of the previous exclusion zone, build up on all the nanoparticles present in the solution. The information gets amplified during this process and shared with all the nanoparticles present in the solution to alter their structure for permanent storage. Iterations can be continued further with advantage till the information is amplified enough to be fully decipherable to biological systems.³⁰

"The Nanoparticle—EZ Shell Model" is successful in explaining homeopathic medicine and its bizarre appearing properties.^{9,30} For example, it is a common observation that homeopathic medicines lose their properties around 70 degrees

C and above. This neutralization can be explained because heat favors EZ growth and excessive heat does so excessively reverting the information containing modified EZ to the generic one. Further, this model also successfully handles 2 big challenges. One is that despite being in extreme dilution, homeopathic medicine is not as sensitive to impurities as it should be. Thus, “This model explains why homeopathy could take birth 2 centuries ago at the time of impure chemistry when Hahnemann even made his medicine occasionally in whisky.”⁷⁴ Another is virtually unlimited shelf-life of homeopathic medicines as, among polar liquids, water forms the thickest EZ, and it cannot be removed from the surface of a hydrophilic nanoparticle at room temperature.

Thus, it is fair to accept that serially diluted succussed solution of a drug/toxic substance, even beyond its physical presence, is bioactive because of nanoparticle-exclusion zone shells present in it, which can carry drug-specific information in an amplified form. A study in conventional nanopharmacology reveals that lactose can act as a “Trojan horse” on nanoparticles to help intracellular delivery through them.⁸⁶ Homeopathic medicines are usually dispensed on lactose (or sucrose).

Independent reviewers have concluded, “there is empirical evidence for physiochemical characteristics of homeopathic preparations (i.e., measurable differences to succussed controls, such as increased UV absorption and increased NMR T1/T2 relaxation time ratios). Further, a number of physical and environmental influences were identified: Differences to controls seem to increase with time, moderate temperature, small sample volume, and in ionic medium, whereas high temperatures seem to abolish differences to controls.”⁸⁷

How Ultra-High Dilutions Can Have Physiological Effects

MIT physicist Seth Lloyd asserts, “Nature is the great nanotechnologist. The chemical machinery that powers biological systems consists of complicated molecules structured at the nanoscale and sub-nanoscale. At these small scales, the dynamics of the chemical machinery is governed by the law of quantum mechanics.”⁸⁸

One potential explanation for how homeopathic medicines provide therapeutic benefits is evidenced by their ability to have an effect on gene expression. Khuda-Bukhsh and colleagues showed the ability of homeopathic medicines to influence gene expression in cancer cells.⁸⁹ Khuda-Bukhsh was quoted in a *Nature India* report as: “Since the homeopathic drugs are very highly diluted, they are non-toxic and could be used as nanomedicines for personalized treatment that depends on the individual genome.”⁹⁰

Bellavite and colleagues found that homeopathic potencies of *Gelsemium sempervirens* modulate the expression of genes involved in neuronal functions.⁹¹ *Gelsemium* is a common homeopathic medicine for certain types of anxiety.

Using whole-genome transcriptomic analysis, Bigagli et al investigated the effects of a range of *Apis mellifica* potencies on gene expression profiles of human cells.⁹² RWPE-1 cells, a

non-neoplastic adult human epithelial prostate cell line, were exposed to varying doses of *Apis mellifica* (i.e., crush bee in the 3C, 5C, 7C, 9C, 12C, 15C, and 30C potencies) or to the resembling placebo solutions for 24 hours. Non-exposed cells were also checked for gene expression variations. Results showed that *Apis mellifica*, in the form of homeopathic potencies, retained the ability to trigger significant variations in gene expression even in extreme dilutions, while reference solvent failed to do so.

The obvious explanation for how ultra-high dilution of a drug/toxic substance can have profound physiological effects stems from evidence that shows that small nanoparticles can readily cross cell membranes and translocate around the body via blood and lymph and can pass through the blood-brain barrier with much greater ease than larger doses.⁹³⁻⁹⁵ When one accounts for these pharmacological effects along with the possible electromagnetic and optical signals that nanoparticles can emit, these cell to cell signaling networks of the body carry out adaptive changes. The induction of endogenous events starts to happen and the usual methods of cell to cell signaling with mediators and nanoscale signals carry out the effects. A broad body of research on hormesis (low dose effects) has shown how low doses of nanoparticles can initiate large (non-linear) changes in bodily responses.²⁸

Recent conventional biomedical research suggests that once in contact with biological fluids, nanoparticles adsorb active biomolecules around them, forming a protein corona. This corona is strongly affected by the patient’s specific disease and accordingly influences the biological fate of nanoparticles, including their pharmacokinetics, biodistribution, and therapeutic efficacy.⁹⁶ In this regard, Tavakol et al even emphasized “the need for the development of patient-specific NPs in a disease type-specific manner for high yielding and safe clinical applications.”⁹⁷ The natural nanoparticle—exclusion zone shells present in the remedy, selected on the basis of the principle of similars, can be such nanoparticles which carry the drug-specific information.

Difference Between Hormesis and Homeopathy: The Principle of Similars

Wiegant and Van Wijk developed the post-conditioning hormesis methodology and unequivocally supported the law of similars at the cellular level.^{15,98} Rattan and Deva realized during their cellular study that a component of the principle of similars is present in hormesis.⁹⁹

Chikramane et al observed hormetic activation at cellular level with metal-based high potency homeopathic medicines.²⁰ These were the commercially made medicines purchased from the market. Chikramane et al found that these medicines contained “a billion-fold lower concentration” of their respective metals than synthetic nanoparticles of the same metals (controls) required to cause hormesis.²⁰ Upadhyay pointed out that at such a low concentration, numerous toxic substances, including some source-drugs of homeopathic medicines, remain present in commercially made medicines.⁷³ Thus, cause of the

observed hormetic activation cannot be the metal but information specific to it.

The Chikramane et al study confirmed that conventional metal-based homeopathic medicines in 30C and 200C potencies which are far beyond Avogadro exhibited hormesis. The relationship between hormesis and homeopathy was suggested as: "Homeopathy is the best known medical analog of hormesis."¹⁰⁰ While homeopathy is a therapeutic system of healing, hormesis is an effect.⁷³ The common thread linking them is that they involve the secondary paradoxical effects of drugs and toxins in biological systems as a function of dose or time.¹⁰⁰ It is important to note that clinical homeopathic practice may be related to pre-and post-conditioning hormesis, when it is for prophylaxis and treatment respectively.⁷³

Hormesis is a basic and general phenomenon. Equipped with the ability to observe the principle of similars, homeopathic phenomenon could be evolved through hormesis as being exclusively therapeutic and deeper in action than hormesis to support life on the toxic Earth.⁹ This is a possible reason why the pre-and post-conditioning hormesis research methodology can help to study homeopathic phenomenon which Hahnemann exploited to establish homeopathy.

Discussion

Presently, there are 4 main working hypotheses/models to explain the bioactivity of serially diluted succussed solutions of a drug/toxic substance used in homeopathy as medicines.

Theoretical physicists Del Giudice and Preparata proposed quantum coherence domains of around 100 nm in diameter in water that could store the source-drug information in the form of electromagnetic frequencies.¹⁰¹ This model could not get sufficient experimental support.¹⁰² Anagnostakos et al hypothesized hydrogen-bonded stable water structures called clathrates in homeopathic medicine to keep the memory of the source-drug.¹⁰³ The clathrate model is speculative, even though the presence of clusters in water is well established. Thus, there was no satisfactory understanding of the observed memory phenomenon.¹⁰²

When Chikramane et al saw nanoparticles of the respective metals in 6 metal-based commercially made homeopathic medicines, they found that the source-drug nanoparticles remained present despite their dilutions and that their presence could lead to the medicines' therapeutic effects.²³ However, as yet, there is no adequate replication of this research to fully confirm its veracity. Further, other observers claim, "there is no convincing evidence that highly diluted homeopathic preparations contain of the starting material."⁸⁷

Upadhyay proposed a nanoparticle-based model to explain the bioactivity of serially diluted succussed solutions of a drug/toxic substance/magnetic field. He called it "The Nanoparticle-Exclusion Zone Shell Model."³⁰ Like the first 2 models, this model is based on "memory" but provides a physical substrate to hold information with the help of exclusion zone. This model suggests that during the first 3 centesimal iterations, the source-drug information is extracted in "crude and condensed" form

by nanoparticle-exclusion zone shells, which later iterations evolve. This model explains the physical existence and properties of magnetized water and homeopathic medicines. As coherent domains of Del Giudice and Preparata can be identified with EZ water,¹⁰⁴ the Nanoparticle-Exclusion Zone Shell Model covers coherent domains model and also clathrate model at least in spirit that "memory" is the cause of the effect.

A nanoparticle-exclusion zone shell can radiate and thus the model based on it can explain the observations like as follows,^{9,30}

1. Vigorously shaken ultra-high dilution of lithium chloride and sodium chloride were irradiated by X-and y-rays at 77 K and then let them warm up to room temperature. Rey claimed, "During that phase, their thermoluminescence has been studied, and it was found that, despite their dilution beyond the Avogadro number, the emitted light was specific of the original salts dissolved initially."¹⁰⁵
2. Nobel Laureate Montagnier and colleagues found that electromagnetic signals were emitted by extremely diluted and vortex-agitated aqueous solutions of DNA, when not even a single DNA molecule was expected to be present.¹⁰⁶

The recent findings suggest that protein corona is strongly affected by the patient's specific disease and gives rise to the personalized protein corona.^{96,97} The nanoparticle-exclusion zone shells, present in the homeopathic medicine selected as a remedy for the patient by observing the law of similars, can be the personalized nanomedicines for the patient. Further, they can be more useful as they are perceived to carry the required source-drug information in an amplified form to communicate through electromagnetic emission.

Even Modern Medicine Is Still Largely Empirical

Before discussing the evidence base for explaining how homeopathic medicines may work, it is important to acknowledge that modern medical science still doesn't know how many of their most commonly prescribed drugs work. For instance, despite the fact that acetaminophen is one of the most popularly prescribed over-the-counter drugs for pain and fever, it is still unknown precisely how it works.¹⁰⁷ Lithium is one of the most commonly prescribed psychiatric drugs over the past 50+ years, and yet, the specific biochemical mechanism of lithium action in stabilizing mood is unknown.¹⁰⁸ Metformin is a first-line medication for the treatment of type 2 diabetes and it has been used in medical care for almost 100 years, and yet, its mechanism of action is incompletely understood. Even drugs for general anesthesia do not have an adequately understood mechanism by which they work.¹⁰⁹

Despite the billions and even hundreds of billions of dollars of sales of each of these drugs, this lack of adequate understanding about how these drugs work doesn't stop physicians

from prescribing them or patients from wanting to take them. This acknowledged humility about present-day ignorance about the action of modern drugs is mentioned here because some skeptics assert that the precise mechanism of action of homeopathic medicines is unknown, and they therefore assert that it should be unethical for health and medical professionals to prescribe homeopathic medicines, and for pharmacies to sell them.¹¹⁰ Such points of view represent a double standard that has no place in medicine or science.

Hormesis and homeopathic phenomena are not well understood at the molecular level, but new and compelling basic sciences research has uncovered reasonable and plausible explanations for how nanoscale effects can have surprisingly remarkable and tangible physiological and health benefits. Upadhyay suggested that some toxins/ chemicals, used in modern medicine as drugs, may be potentized effectively.⁹ If this happens, it would diffuse the boundary between modern medicine and homeopathy.

Randomized, placebo-controlled, double-blind clinical trials or their types are necessarily required to test for the efficacy of a medicine. Such trials especially become more critical as medicines are still mostly empirical. These trials are developed to test the effectiveness of modern medicine. But homeopathy is a highly individualistic therapy, and these trials cannot do justice to it. It has unnecessarily been criticized as a placebo therapy based on these trials, even suggesting its end in an editorial in *The Lancet*.¹¹¹ However, later, the same journal admitted that its practice is booming,¹¹² and other more recent and more comprehensive reviews of clinical research in homeopathy have confirmed more efficacy than that of a placebo.³¹⁻³³ The challenge to the proper scientific assessment of homeopathic medicine is that the methods used to evaluate it must be in line with the individualized prescriptions that lie at the basis of this medical system.

Conclusions

Water has been anomalous, and scientific understanding about it is increasing. Further, the activities of nature at the nanoscale are now becoming more evident. The biological activity of serially diluted succussed solutions, even beyond the physical presence of solute, now seems scientifically plausible. Silica is ubiquitous and also leeches from glass walls of bottles. Nanoparticles rich in silicon remain present in such solutions. In presence of oxygen, the extra pressure caused by violent strokes facilitates exclusion zone build upon these hydrophilic nanoparticles as interfacial water. During this process, nanoparticle and exclusion zone duo as nanoparticle-exclusion zone shell can pick up the source-drug specific information in “crude and condensed” form and then amplify it during further iterations. Thus, such dilutions as medicines can be more effective than source-drug itself and if it is not hormetic, such dilutions can be so. The nanoparticle—exclusion zone shells present in the remedy for a patient, selected on the basis of the principle of similars, can be his personalized nanoparticles to interact with

his personalized protein corona for the best possible therapeutic effects with least side effects.

Thus, “The Nanoparticle—Exclusion Zone Shell Model” has been identified as the possible potential mechanism of bioactivity of serially diluted succussed solutions even beyond Avogadro. This model provides a physical substrate to hold memory with the help of exclusion zone and thus contains the spirit of clathrate and quantum coherence domains models that such dilutions have source-drug information. The froth floatation hypothesis, on the other hand, of retaining source-drug irrespective of its dilution level may be only partially explanatory.

Hormesis can also be observed with homeopathically prepared ultra-high dilutions. As such, the difference between hormesis and the homeopathic phenomenon seems to be that of the principle of similars, which makes the latter specifically therapeutic. Thus, hormesis is a basic phenomenon.

Despite the fact that medical science today represents the epitome of progress in the provision of health and medical care, it is widely recognized that there are gaping holes and even significant dangers in serving the health needs of people young and old when only conventional medical treatments are provided. Although considerably more research is necessary before making firm judgments about homeopathy, it is reasonable for health and medical professionals, public health experts, and patients to explore and test what role homeopathic medicines should play in our comprehensive health care systems.

Clinical trials, as used in modern medicine, should be modified in a way they could be able to test the efficacy of the hormetic or homeopathic medicines. These trials are not only essential to adequately and accurately assess these medical interventions but also are important to convince the general public and policymakers of how much homeopathy and hormesis have a place in medicine and science.

After much reluctance, hormesis concept has now become well established in biomedical science as a genuine phenomenon of nature.¹¹³ Similarly, it seems, it may soon accept homeopathy as a system of nanomedicine, though more investigations with independent replication must be conducted for more widespread acceptance to take place.

While synthetic nanomedicine carries drug material to the target inside the organism under reductionist approach, homeopathic nanomedicines seem to carry drug-specific information in an amplified form to the organism under the holistic approach. The work presented here would also encourage research work in hormesis beyond Avogadro’s limit. Nature at nanoscale seems to be more mysterious than thought. It is only a matter of time when new nanoscale technologies would be utilized in a wide variety of fields, including medicine, and then various portrayals of the future as epitomized in science fiction could become reality.

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