Laboratory Research in Homeopathy: Pro

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Homeopathy is a holistic method of treatment that uses ultralow doses of highly diluted natural substances originating from plants, minerals, or animals and is based on the principle of "like cures like." Despite being occasionally challenged for its scientific validity and mechanism of action, homeopathy continues to enjoy the confidence of millions of patients around the world who opt for this mode of treatment. Contrary to skeptics' views, research on homeopathy using modern tools mostly tends to support its efficacy and advocates new ideas toward understanding its mechanism of action. As part of a Point-Counterpoint feature, this review and its companion piece in this issue by Moffett et al (*Integr Cancer Ther*. 2006;5:333-342) are composed of a thesis section, a response section in reaction to the companion thesis, and a rebuttal section to address issues raised in the companion response.

Keywords: *homeopathy; potentized remedy; ultrahigh dilution; laboratory research; mechanism of action; gene regulatory switch*

Thesis

In 1790, about 216 years ago, a German physician named Samuel Hahnemann (1755-1843) noticed during experimentation on himself that after taking the malaria remedy China (Peruvian Bark), he experienced symptoms similar to those of patients with malaria. Similar tests (later termed "provings" in English and "Arzneimittelprufüngen" in German) were repeated on himself, his family, and friends, and the basic principle "similia similibus curentur" or "like cures like" was apparently confirmed. The results of these large-scale provings led Hahnemann to conclude that if a compound caused symptoms in healthy volunteers, it should then also serve as a remedy for patients who actually suffer from such symptoms. In the course of his experiments, Hahnemann further noticed with great interest that diluting and vigorously shaking his remedies (a process later termed as "potentization" or "potentiation") often rendered the remedy more potent in terms of clinical response. Soon this method of treatment with extremely low doses (ultralow doses) became popular. This was a period when very crude methods like application of heat and cold, blood letting, and crude surgeries without proper anesthesia were largely practiced, and often such treatments brought more pain to the patients than their suffering attributable to diseases. It was no wonder that homeopathy initially proved to be a revolutionary and successful mode of treatment and therefore received wide acceptance throughout the world up to the end of the 19th century.[1] However, homeopathy started facing stiff opposition from rationalists as well as scientists that led to its rapid and sharp decline, yielding room to various other modes of treatment considered to have a more sound scientific footing. The greatest objections to homeopathy and one of the most powerful arguments that caused the apparent downfall of homeopathy lie with the potentization and dilution procedure of the homeopathic medicines.*

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What Are Homeopathic Remedies?

Most homeopathic remedies are derived from natural substances that come from plants, minerals, or animals. A remedy is prepared by diluting and succussing the substance in a series of steps. Homeopathy asserts that this process can maintain a substance's healing properties regardless of how many times it has been diluted. Remedies are sold in liquid, pellet, and tablet forms. There are certain dietary restrictions (eg, raw onion and garlic are not permitted to be taken during

*In the homeopathic potentization procedure, 1 mL of the mother tincture is generally diluted with 99 mL of ethanol (40-90%) and given 10 "succussions" (a vigorous type of shaking either by hand or machine) to produce the potency I C. Similarly, 1 mL of the drug solution at potency 1 C is again added with 99 mL of ethanol and followed by 10 succussions given to produce the potency 2 C and in this way by successive dilutions, further potencies like 30 C, 200 C, and beyond, are produced. Therefore, at high dilutions, say beyond potency 12 C (beyond Avogadro's limit, ie, 10^{-23}), the solution is unlikely to contain even a single molecule of the original drug material (ie, the mother tincture).

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the course of homeopathic treatment); any food should preferably be taken at least 1 hour before or after taking homeopathic remedy. Alternatively, some practitioners tell the patients to avoid only those foods to which they react strongly on an individualized basis.

Basic Tenets of Homeopathy and the Bone of Contention

Hahnemann was perhaps not aware of the consequences of homeopathic dilutions in the context of Avogadro's limit, but he believed that "vital force" of a substance was somehow released by the process of "succussion" to the "vehicle," which now behaved as the medicine.

In fact, of the 3 homeopathic principles postulated by Hahnemann, namely, (1) like cures like, (2) one remedy at a time, and (3) increasing efficacy with increasing dilution, the third became a target of vehement attack, primarily because in the present state of our knowledge, it is indeed difficult to explain how any drug can have medicinal property and clinical efficacy without having even a single molecule of the original drug substance; the proposed concept of "higher the dilutions stronger the medicine" is thus found to be scientifically unlikely. Notwithstanding repeated provings of several homeopathic remedies carried out by Hahnemann and his disciples[2,3] on both healthy and diseased human subjects, the challengers were not convinced and questioned the validity of such experiments in the light of modern scientific standards. They went on to argue that patients who were cured by homeopathic remedies could very well have been cured without any medicine at all, or the cure was just an effect of their belief in the medicinal efficacy, that is, simply attributable to "placebo effect." When it is pointed out that homeopathy acts equally effectively in babies and animals, who have no belief or faith in the medicine, challengers also demand a valid explanation for the mechanism of action of the ultralow doses of medicines that could be acceptable within the realm of known scientific knowledge. Thus, homeopathy suffered a period of ignominy but still survived with the believers continuing to support this benign method of apparently effective treatment. But the stage was now set for beginning serious research on homeopathy, initially for proving the efficacy and thereafter for explaining the mechanism of action of the highly diluted remedies, although the attacks[4] and rebuttals[5-7] continue.

Does Research on Homeopathy Need Special Considerations?

Doing research on homeopathy within accepted scientific norms has some inherent methodological difficulties. For example, there is no fixed medicine for any particular disease in homeopathy, but there are particular medicines for particular sets of symptoms. The individualized disease symptoms rather than the disease itself are primary in the selection of the specific drug. Furthermore, in the selection of a homeopathic remedy, "mind" and "general constitution" are also given due importance, particularly in cases of chronic disease. Therefore, the remedy may be different not only for the same disease but also for 2 persons suffering from the same disease, who differ in some specific symptoms. In fact, a particular medicine is to be selected critically based on totality of symptoms. For example, 3 patients with influenza may differ in 2 symptoms in the following manner: patient 1 is very restless and frequently wants to take a little water; patient 2 is not restless, prefers to stay quiet, and wants to take a large amount of water less frequently; and patient 3 is not restless, lies in bed semiconscious, does not like to talk with anybody, and has no thirst. Rhus toxicodendron (or Arsenicum album) is the most suitable remedy for patient 1, Bryonia alba for patient 2, and Gelsemium nitidum (or Gelsemium sempervirens) for patient 3. Another influenza patient with a high temperature with a red face and throbbing headache may require yet another remedy, Belladonna. A clinical trial on influenza patients to determine the efficacy of any particular remedy, say, Rhus toxicodendron or Gelsemium, may not find that all influenza patients respond equally well. Thus, the first difficulty in carrying out scientific clinical trials (randomized clinical trials)[8] is the problem of selecting 1 among several drugs for the same disease, which may not actually be the "most suitable" drug for all. Because there is not a single specific treatment for a single disease, the conventional form of clinical trials would demand clinical trials for sets of symptoms and corresponding remedies used in homeopathy in order to show causal efficacy for all of them.[9] Thus, to find out whether a homeopathic approach is comparable or superior to a standard treatment in general for all sorts of patients, a rather cumbersome randomized comparison study would be called for. The question to be answered by a double-blind randomized control trial with placebo (ie, the "vehicle" of the drug) is whether the homeopathic remedies as such are superior in efficacy to placebo. In human trials, ethical issues in administering placebo to ailing people with chronic or serious diseases also need consideration.[10] It can be difficult to establish the causal efficacy of homeopathic remedies above placebo because of such considerations, necessitating meta-analysis of controlled clinical trials to arrive at a conclusion of either positive clinical effect of a drug over placebo on human subjects with any given disease (ie, similar set of symptoms) or no such effect. Summary tables of clinical trials in homeopathy as well

as systematic reviews of homeopathy in general and on single medical conditions can be found on the Web site of the U.S. National Center for Complementary and Alternative Medicine (http://nccam.nih.gov/health/homeopathy/).[4,11-27]

Is Understanding Homeopathy a Simple Task?

No, not really. Other difficulties exist in conducting research leading to understanding of pathways/mechanisms of action of homeopathic drugs, particularly the potencies above Avogadro's limit (ie, above potency 12 C). The physical absence of original drug molecules in these higher potencies makes it extremely difficult, indeed, almost impossible, to keep track of the drug molecule, even if it is prepared from an isotopic element (say, potency 30 of isotopic sulfur), within the animal body after its oral administration. This prevents the researcher from following the exact route of movement of drug substance in relation to time, which in other orthodox systems is quite possible.

Another difficulty is the need for research in at least 3 different disciplines of science—physics, biology (particularly neurobiology, immunobiology, and molecular biology), and medicine—to understand the complete mechanism of action of homeopathic remedies. Knowledge in physics is necessary for understanding how the medicinal property is transferred to and retained in the vehicle and becomes active when administered in miniscule doses. At the biological level, an explanation is needed for the extraordinary sensitivity or receptor function, including a mechanism that works according to Hahnemann's basic simile and potency rules. Medicine is needed to understand clinical efficacy, taking the main role in understanding placebo effects and similar "mind–body" interactions. The decisive point of homeopathy is therefore the argument that homeopathic remedies are not solutions but rather succussions of the efficient/drug substance (or imprints instead of mixtures in the case of sugar "globuli" commonly used in the clinic as a vehicle for homeopathic remedies).[28]

Can Existing Literature on Homeopathy Research Answer Some Uncomfortable but Pertinent Questions?

Transfer of Medicinal Property to Vehicle: Some Physical Concepts Based on Research.

There are some excellent working hypotheses to explain how the specific organization of solvents is able to retain and maintain some properties of the initial substance. A few prominent models are discussed below. A clathrate model based on dielectric and differential scanning calorimetric measurements has been proposed[29] to explain how medicinal properties can be transferred to "vehicle," and possible physicochemical differences between homeopathic dilutions and the corresponding solvent can be predicted. Some clathrates exist even if their core molecules are removed or exchanged for solvent molecules. Since clathrates may behave like crystals, they may replicate themselves during the homeopathic dilution process in a similar way to crystal growth. Allegre et al[30] suggested that the observed oscillation of the effectiveness of homeopathic solutions at different points in the serial dilution process might be similar to the oscillatory nature of crystal growth.

The leading current proposal for the mode of action of such "ultramolecular" dilutions is that water is capable of storing information relating to substances with which it has previously been in contact and subsequently transmits this information to presensitized biosystems. The process is thought to be mediated by structural modifications of water, analogous to the storage of information by magnetic media. Such information is retained in physical, rather than chemical, form.[31]

Studies on molecular clustering in water solutions showed that as a solution is made more and more dilute, larger, very stable aggregates develop.[32] This means that residual molecular clusters of original substance might be present in homeopathic dilutions.

Davydov,[33] who investigated solitons (a soliton is a self-replicating solitary wave caused by a delicate balance between nonlinear and dispersive effects in the medium), postulated a "soliton excitation model" suggesting that homeopathic drugs acted like solitons, which are responsible for high-temperature superconductivity as well as for the well-known extraordinary sensitivity of biological systems.

Contrary to what skeptics of homeopathy have asserted time and again, that there is "nothing" in the medicines because there are few or no molecules left in the highly diluted solutions, Elia and Niccoli[34] published their observations that strongly suggest there may be "something" active in homeopathic medicines. These authors measured the amount of heat emanating from plain double-distilled water and compared that with double-distilled water in which a substance was placed. Both the control water and the treated water underwent consecutive dilutions between 1 and 30 times, with vigorous shaking between each dilution, representing the common pharmacological method by which homeopathic medicines are made. The authors conducted more than 500 experiments, approximately half made with double-distilled water that was mixed with a specific acid (vinegar) and base substance (sodium chloride) and half in the control group of only double-distilled water. The researchers found that 92% of the

test solutions with the added acid or base substance had higher than expected heat emanating from them. The authors claimed that their results strongly support the hypothesis of the existence of a memory of water, advocated earlier by Davenas et al[35] in their controversial article on basophil degranulation. In a multiple-center trial repeating that of Davenas et al, Belon et al[36] obtained results to suggest inhibition of human basophil degranulation by homeopathic dilutions of histamine. Lo[37] found that substances that were sequentially diluted in double-distilled water at least 6 times and then shaken in between would create water clusters or ice crystals ("I_E crystals") that maintained an electrical field and did not melt in room temperature water.

Furthermore, structural differences between nuclear magnetic resonance spectra or Fourier transform infrared spectra of homeopathic potencies and their solvent ethanol have also been demonstrated.[38,39] Rey[40] produced evidence that ultra dilutions also contain initial properties of original salts that can alter chemical and biological properties. They demonstrated that despite their dilution beyond Avogadro's number, the emitted light from ultra dilutions of lithium chloride and sodium chloride was specific to the original salts dissolved initially. Thus, some physical properties (like thermoluminescence) of the initial substance can be retained even after the dilution of the substance beyond Avogadro's number. However, the contention that digital signals recorded on a computer disk produce specific biological signals was not confirmed in a replication trial.[41]

Admittedly, there still remains some uncertainty about details of water structure, and further in-depth studies are necessary to provide deeper insight into the nature of this substance, which may further our understanding of the philosophy and science of homeopathic potentization.

Homeopathic Remedies and Biological Responses: a Few Prominent Laboratory Studies.

What happens after the homeopathic remedy is administered on the tongue of patients and how the remedy removes disease symptoms have remained areas of hot debate, although several hypotheses exist.

Davenas et al[35] hypothesized the existence of drug substance in ultradiluted remedy in the form of "molecular imprints" or as "memory" molecules that were capable of inducing changes at the level of the body's defenses.

Studies on crystal-induced inflammation as well as insulin-receptor activation by oxyanions have been used to understand how the hydrate structure of certain types of silica or some anesthetic agents could activate specific types of cell surface proteins directly or indirectly, attributable to their coincidental complementary structures.[42,43] Research conducted by several others has tested the biological effects of I_E crystals and has found remarkable effects. Lo and Bonavida[44] tested a sample of crystals on blood and found a 2- to 100-fold increase in cytokines (mediators of immune function that protect against infection and tumor growth). Important signal transduction studies are being carried out in other institutions.

The term *hormesis* (meaning excitation by an impulse) is often used to describe "a stimulatory effect of subinhibitory concentrations of any toxic substance on an organism." Stebbing[45] used this term to describe the stimulation of growth by low levels of inhibitors. Extensive in vitro studies have been carried out at the University of Utrecht using cultured mammalian cells in homeopathy research to reveal the underlying molecular mechanisms of hormesis.[46] According to these researchers,[46-48] "the stimulation of a disturbed self-recovery by the application of the similia principle is considered to be the essence of homeopathy." Interestingly, altered levels of messenger RNA for heat shock protein were found to be produced by micro-dose treatment used per the similia priniciple.[47]

Khuda-Bukhsh[49,50] proposed a hypothesis based on evidence that potentized homeopathic drugs acted through regulation of relevant gene expression in amelioration and cure of disease symptoms. According to this hypothesis, homeopathic remedies carry specific "signals"[51] that can be identified by the receptor cells and that can act as triggers for switching "on" or "off" certain relevant genes (perhaps through micro-RNA or the signal transduction system), the functions of which had gone awry in the diseased state. The "trigger" initiates a cascade of gene actions to bring them back to their normal functioning, which eventually lead to the ameliorative and curative changes that are observed after the administration of these remedies. The signals could act as "effector" or "silencer" molecules and could activate expression of many downstream proteins through a chain or cascade of reactions.

In Vivo Laboratory Experiments and a Few Other Hypotheses on Biological Response.

Aguejouf et al[52] demonstrated thromboembolic complications to persist for several days after a single-dose administration of homeopathically potentized aspirin in Wistar rats subjected to experimental thrombosis induced by laser beams. Subsequently, this group[53] also demonstrated a potent antithromboembolic effect of potentized acetyl salicyclic acid in similarly induced experimental thrombosis. Researchers in Germany have observed an inhibitory effect of

ultradiluted dichlorophenol on the bacterium *Vibrio fischeri*.[54]

Homeopathic apis and histamine have a significant effect on reducing the release of certain allergy-causing chemicals from basophils, which demonstrates a possible reason for homeopathy's positive effects on allergies.[55]

Many controlled laboratory experiments in vivo have been conducted by using mammalian models like mice and rats and occasionally other higher mammals like cattle or horses. All these experiments apparently support the positive efficacy of potentized homeopathic remedies, in protection from radiation,[56-58] toxic chemicals,[51,59-66] or carcinogens[67-71] or in human cancer.[72] The mechanisms of radiation-induced DNA/ chromosome damage are well known, and equally well known are the genetic mechanisms by which damaged DNA and chromosomes are retrieved and repaired[73]; the same is also true for the effects of various toxic chemicals and carcinogens on living systems. All these studies reveal that homeopathic remedies can act at molecular, subcellular, cellular, and physiological levels and can effectively enhance the DNA repair process, which involves active participation of some specific genes. Incidentally, if transcription blockers are used along with the chemical/physical mutagens,[62,74] the efficacy of the homeopathic drug is effectively reduced, indicating active transcription as a precondition for homeopathic action.

Unfortunately, however, most of the work carried out in our laboratory has not yet been replicated by any other group, presumably because the studies involved many biological parameters from diverse disciplines like cytogenetics, biochemistry, hematology, and electron microscopy. We strongly encourage that these studies be replicated by individual researchers, who we hope can provide new clues to homeopathic mechanisms. Particular implications of the gene expression hypothesis that need experimental exploration are the following: First, the expression of genes does not necessarily depend on the physical existence of any drug molecule but can be triggered at the sight, smell, touch, or even thought of something that is already stored in one's "memory." For example, the expression of "anger" genes (serotonin transporter gene) can be stimulated/activated by a slap (touch stimulus), abusive language (auditory stimulus), showing red eyes (optic stimulus), or even a thought of an earlier insult (thought stimulus). Second, evidence of some "early response genes," which act in a fast and transient manner in response to different physical, chemical, or environmental stresses, has been published.[46] Third, the hypothesis can explain the positive action of potentized homeopathic drugs reported in animals (having a central nervous system capable of sending signals through synapses) and plants and microbes (without having a defined central nervous system). Fourth, only orderly expression of genes in cascade or chain reactions can explain how an ultralow dose of highly diluted (potentized) homeopathic remedy can have ameliorative changes covering multiple organs simultaneously and even can act on "mind," governed essentially by specific genes. Fifth, the hypothesis clarifies the significance and necessity of some intercurrent "constitutional" remedies in chronic cases that may have specific action on suitably modifying a specific "genetic makeup" ("constitution" of Hahnemann) that will render the symptomatic remedies more active.

Although many questions remain pertaining to the way and level at which the specific genetic expression can be normalized, this hypothesis, still highly speculative, needs the critical attention of researchers, because from embryonic development until death (or apoptosis at the cellular level), all important development, growth, metabolism, and repair mechanisms are under strict genetic regulation and control. It is only when this precise regulatory control is lost that disease symptoms appear, a glaring example being cancer, which is primarily produced by the loss of genetic control of cell division. Similarly, bacterial or viral infections can also cause a temporary breakdown in the genetic regulatory mechanism.

Clinical Reports and Some Popular Views on Homeopathy

There are many clinical reports of the efficacious use of homeopathic medicines in a variety of diseases.[75] Many homeopathic practitioners are not concerned about the fact that they owe patients an explanation as to how these medicines actually act; they consider that it is irrelevant so long as they can cure people of their ailments. Some people believe that if homeopathy appears to be helpful and safe, then scientifically valid explanations or proofs of this alternative system of medicine are not necessary. There is a point of view that homeopathy does work, but that modern scientific methods have not yet explained why and how.

Is Homeopathy an Example of the Placebo Effect?

The placebo effect is a well-documented medical phenomenon. Placebo effects are believed to be mediated by both cognitive and conditioning mechanisms. Until recently, little was known about the role of these mechanisms in different circumstances. Now, research has shown that placebo responses are mediated by conditioning when unconscious physiological

functions such as hormonal secretion are involved, whereas they are mediated by expectation when conscious physiological processes such as pain and motor performance come into play, even though a conditioning procedure is carried out.[76] Evidence indicates that the placebo effect in patients with Parkinson's disease is powerful and is mediated through activation of the nigrostriatal dopamine system, the system that is damaged in Parkinson's disease. This result suggests that the placebo response involves the secretion of dopamine, which is known to be important in a number of other reinforcing and rewarding conditions, and that there may be mind–body strategies that could be used in patients with Parkinson's disease in lieu of or in addition to treatment with dopamine-releasing drugs. Finally, future research focusing on basic mind–body mechanisms and individual differences in responses is likely to yield new insights that may enhance the effectiveness and individual tailoring of mind–body interventions. In the meantime, there is considerable evidence that mind–body interventions have positive effects on psychological functioning and quality of life and may be particularly helpful for patients coping with chronic illness and in need of palliative care. Placebo administration is also known to affect the brain both in pain and in Parkinson's disease.[77] Often, patients taking pills will feel better, regardless of what the pills contain, simply because they believe the pills will work. Could then the beneficial effects of homeopathy be entirely attributable to the placebo effect? No—numerous double-blind placebo-controlled experiments convincingly show that effects produced by the homeopathic remedies are greater than those of placebo alone.

Scope of Further Research

Homeopathy has survived more than 200 years. There is a resurgence of interest in homeopathy, despite the periodic challenge it faces. Certain areas of research seem to be crucial in deciding the fate of homeopathy. Apart from the important areas of immunology and toxicology, extensive research should be done in areas of cell receptors, gene expression, and signal transduction pathways using suitable model systems both in vitro and in vivo. Already some fruitful research has been initiated in the field of receptor and cytokine pathways, but more research in this direction is warranted. There is scope for testing its relationship with micro-RNA, which has opened up new vistas of gene expression. Only 3% to 5% of the human genome is ever expressed; what new regulatory activities of the genome may be hidden in the remaining 95% is a matter for future research to disclose.

Concluding Remarks

Finally, to conclude, a few points may be raised to ponder:

First, why should there be disagreement in several critically performed analyses and meta-analyses? Is it because of some fallacy in methodology, application, or interpretation? If it is resolved that homeopathy acts, as evidenced by some well-designed experiments and clinical trials, then there must be an underlying mechanism of action, which may need more vigorous research to be well understood. Instead of trying to negate the results of well-conducted experiments, challengers should become involved in active research to verify results of tests conducted by others, without any bias for or against homeopathy, but keeping in mind the special considerations needed for homeopathic research. The dietary rules of homeopathy should also be kept in mind when carrying out experiments with homeopathic remedies.

Second, special efforts should be directed to testing the efficacy of homeopathic drugs known to combat cancer and other difficult diseases, so that their use may be recommended initially as a supportive medicine alongside orthodox medicines to improve quality of life.

Third, this system of medicine, which has passed the test of time and has rendered service to hundreds of thousand of people in some 40-odd countries, deserves a more systematic approach toward understanding its basic tenets, facilitating its use with a greater degree of confidence by those who prefer this mode of treatment. We hope that more scientists will become involved in homeopathy research with open minds and that premier institutions will encourage research in this area. It is good news that some have already come forward with such aims and objectives.

Response

I will proceed by responding directly to several points made by Moffett et al.

Modern medicine has shifted from countering the symptoms of a disease to disrupting pathophysiological processes, for example, by the treatment of bacterial infection with antibiotics.

It is true that antibiotics have proved to be indispensable for certain emergency situations of bacterial infections, but almost all antibiotics have been reported to have undesirable genotoxic and cytotoxic effects (which are often ignored as "side effects" on the grounds of the greater interest of killing the causal organism) and also have adverse effects on some beneficial microbes residing as commensals or symbionts. The indiscriminate and injudicious use of antibiotics

has been a major cause of the emergence of drug resistance to most antibiotics, which may put the success of one antibiotic in jeopardy at a critical moment, so that the patient has to be treated experimentally with some other antibiotic to obtain the desired effect. For example, in case of renal infection by *Escherichia coli*, sensitivity tests often reveal that the bacteria are resistant to all but 1 or 2 specific antibiotics. The same is true for typhoid. In fact, all new forms of resistant bacteria by and large owe their origin, directly or indirectly, to antibiotic treatment. On the other hand, homeopathic remedies are prescribed based on the totality of symptoms. The homeopathic remedies cannot kill the causal organism as such but may selectively create a physiological microenvironment unsuitable to sustain microbial infection by a yet unknown mechanism, perhaps by changing pH, by making conformational changes on cell surface/membrane/receptors of host or parasite, or by optimizing the body's own defense systems. However, selection of the right homeopathic remedy is extremely important in homeopathy, particularly in combating severe bacterial diseases; sometimes, depending on symptoms, more than 1 homeopathic remedy may be indicated to effect a cure. Therefore, particularly in the treatment of the virulent life-threatening forms, homeopathy is not advisable and should only be used with extreme caution, if at all. The safety of the patient should be borne foremost in mind. However, homeopathy is also often useful for infections in patients who cannot or do not wish to take antibiotics because of multiple drug allergies or chemical sensitivities.

It is claimed that the succussion process "potentizes" homeopathic preparations and that the further the solution is diluted and "succussed," the more effective it will be. These ideas were based on anecdotal observations, not on scientific data.

This area of concern emerges out of the present incomplete state of our knowledge in science and the lack of extensive experimental studies to prove or disprove this concept. However, our experiences with remedies diluted to obtain the 30th and 200th potencies[62,65,66,70] are indicative of the fact that the 200th potency generally acts better, particularly at longer intervals of fixation, than the 30th potency, in mice. However, more such comparative studies on the efficacy of the remedy in different dilutions are warranted to come to a definite conclusion, although in numerous clinical practices the efficacy of higher potencies in curing chronic diseases has been documented, albeit mostly in various homeopathy journals.

Mathematical calculations of water cluster stability in pure water at room temperature suggest that ordered water clusters would be very short lived in solution in the absence of solutes. . . . The water cluster theory of homeopathy runs into additional trouble in light of the fact that many homeopathic preparations are soaked into sugar pills, which are then dried to remove the water.

It's true that the 3-dimensional structure of pure liquid water loses its memory of molecular arrangement through the H-bond network within a very short time. Therefore, the efficacy of homeopathic potency made in pure water may indeed be very short lived. But one must keep in mind that pure water cannot be comparable to a homeopathic potency that is prepared by successive dilution and succussion from a mother tincture and preserved in 90% ethanol. Ethanol molecules with large nonpolar parts can preserve or promote water structures specific to homeopathic potency. An electrostatic component is usually the dominant force contributing to H-bonding. Succussion or any mechanical agitation would therefore make the H-bonding stronger in homeopathic potency. In ethanol solution, it has already been shown that sequential H-bond dissociation and reassociation can occur between the same OH groups. There is also some evidence that the broken bonds in water can reform to give the same H-bond. Further, dissociation is an extremely rare event, with a probability of only 1×10^{16}. Therefore, clusters can persist much longer times (see Sukul et al[39]). I accept that there are some enigmatic areas regarding the physicochemical structure of aqueous ethanol, the vehicle of the homeopathic remedies.

Recently, Sukul et al[39] also explained how the medicinal property can also be retained on sugar globules for a long time. These authors made Fourier transform infrared spectra analysis of potassium bromide powder soaked with a few potencies of several homeopathic remedies and showed that these powders could retain their specific spectral absorption properties, thereby implying that sugar globules could in the same way preserve therapeutic properties of the homeopathic remedies. Homeopathic globules put on the tongue are dissolved in saliva and again enter a watery medium. Sometimes globules are put in water before oral administration.

More in-depth research is warranted to produce further conclusive evidence on the actual mechanism involved in transfer to and retention of medicinal properties in sugar globules. This could be a challenging area for future workers.

Silicates leaching from the glass vials used to make the preparations may be responsible for some differences observed in relaxation times between different solutions.

I agree that some nanoparticles, such as silicon, boron, or the like, could be present in the homeopathic preparations made in glass containers, but I do

not agree that these particles could have the specific medicinal property or biological activity (although they could in some way be implicated in the placebo effect). Had that been so, there could be only 1 panacea in homeopathy, the potentized alcohol, which having reacted with the glass, as has been suggested, obtained the ability to combat every disease. But this is not the case. In our research, the control group fed alcohol-30 (potentized in the same way as the verum, but without the starting drug substance) failed to elicit the same protective results as in the verum-fed series. The efficacy of homeopathic medicines is said to be very specific for a typical set of symptoms, and any remedy not corresponding to these symptoms fails to show removal of the disease symptoms. Thus, along with the nanoparticles there must be some kind of information such as "replicas" or "imprints" of the original drug substance, which could act as the molecular "signal" (the physicochemical nature of which still remains unclear). Furthermore, that the signals emanated from different remedies are different and that the responsive cells can correctly identify and react to them can be substantiated from the clinical observations that a Rhus Tox patient does not respond to another unsuitable remedy, say, Nux Vomica (or for that matter, even a complementary remedy like Gelsemium). Therefore, the signals can be selectively recognized by the receptors (conformationally changed during the disease state?) and can thus trigger the appropriate gene action and subsequent cascade of gene actions following the trigger. Incidentally, the role of nanoparticles and trace elements, once not given due importance in biological activities, is now accepted as of considerable importance, and research on nanoparticles in medicine, particularly in cancer, is gearing up.

In the first attempt to confirm the positive results obtained in the other laboratory, 1 x 10^6 melanoma cells each were injected into 20 mice through lateral tail vein as described by the other laboratory's protocol. Ten animals (control) were given oral administration of 50 µL each of PBS on the same day and continued for 10 days, and the other 10 animals (treated) received the same volume of a homeopathic preparation designated as "1M Thuja" for 10 days.". . . There were no differences between the control and treated groups.

This kind of experimentation results from lack of understanding of the actual protocols to be used for evaluating efficacy of homeopathic remedies. Homeopathic remedies are only capable of removing disease symptoms through all the defense and repair mechanisms available under the command of the living organism. It thus simply reinforces the correct functioning of the regulatory mechanisms in order to optimize functioning of relevant organs/glands necessary for combating disease. Incidentally, Hahnemann also emphasized the role of "vitality" and "vital forces" available to the remedy to accelerate the healing process to the optimum, bringing about complete recovery and normal functioning. Now let us analyze the protocol in question. The strain of mice used, C57BL/6, is widely used in cancer research for some selected advantages. But nevertheless, this is a mutated variety that is genetically modified (deficient in certain metabolic activities and susceptible to various infections and diseases like diabetes and cancer) and is prone to develop melanoma at the slightest provocation (injection with B16F10 melanoma cells). This strain of mice was used and a quite large inoculation of lung cancer cells was made through intravenous injections. Thuja 1M is generally used as a constitutional remedy and has been known to have proven ability in removing certain solid tumors, particularly moles. Other remedies are considered to be more suitable for symptoms of lung cancer. The potency used is also important in acute cases. The results of this experiment appear to have disproved the efficacy of this homeopathic drug's protective abilities. However, several questions arise. What was the result of any allopathic drug used as a control in this case? Was it efficacious in prolonging the life span of mice in the treated group? By analogy, would it be prudent to test the protective efficacy of a known allopathic drug showing an unspecific antidotal effect against poisoning by prefeeding or postfeeding mice sodium cyanide at lethal doses and expecting them all to survive? Research on homeopathy should be done on mice that preferably have not been made genetically deficient for carrying out various metabolic activities, because homeopathy is claimed to activate nonfunctioning (repressed) genes, but not nonexistent ones. In my opinion, even cell cultures, particularly cancer cell lines, which undergo occasional genetic changes after several cycles may not prove to be a suitable tool for homeopathy research. Homeopathic remedies may prove to be more efficacious in controlled experiments carried out on normal inbred mice in vivo provided optimum laboratory conditions.

It should be mentioned that water purification plants had been installed. . . . It is possible that some of the improvements in blood enzyme levels and other parameters could have been due to withdrawal of arsenic exposure.

True, some of the improvements could have indeed been attributable to water purification, but definitely not all. Had that been so, the placebo group would also show similar improvement, which was not the case. Further- more, as we mentioned, the study subjects were continually at risk for arsenic

intake through diet (various crops and cereals in arsenic-contaminated regions also contain considerable amount of arsenic). Therefore, supplying arsenic-free drinking water alone may not be enough to prevent arsenic intake from other sources in these villagers. Visible changes, for example, in the appetite, skin symptoms, and blood parameters in the verum-fed group, were clearly noted. We encourage others to repeat the experiment, either on a mammalian model or on humans, to verify the results.

These studies were conducted in areas of India where groundwater arsenic is common. . . . They were funded in part by Boiron, one of the world's largest producers of commercial homeopathic preparations.

Dr. Moffett and colleagues have raised an interesting issue of funding homeopathic research by "the world's largest producers of commercial homeopathic preparations." In fact, one reason why research on homeopathy has so far been less than optimal is that homeopathy research is seldom funded by government agencies in most countries and mainly has depended on the meager grant funding from either homeopathic drug companies or homeopathic private organizations. If a comparison is made between funds available for homeopathy research and research on orthodox medicines, the funding levels for homeopathy appears, in fact, homeopathic! In addition to huge governmental support, multinational allopathic drug companies like Pfizer or Glaxo not only have their own research and development arms but also give liberal funding for research in their own interest, for which there are too few raised eyebrows. This is one reason why the orthodox system has been able to forge ahead in research compared with other systems of treatment.

Homeopathy trials require the use of positive pharmacological controls as well as negative vehicle controls. It is important to determine the degree to which homeopathic preparations are as effective as known pharmacological agents.

I agree on this count. But I'll add that the side effects of the positive pharmacological control should also be taken into consideration, so that the desirable effect and the undesirable side effects of the drug may be judged vis-à-vis the homeopathic remedy.

There is no way to determine the potency of homeopathic preparations because there are no bioassays or tests that can be used to define potency. Homeopathic preparations are produced in a stereotypical fashion and used without any means of determining if they have been made correctly or not.

I agree. There should be stringent quality control for preparation and distribution of homeopathic drugs to retail shops.

Homeopathic researchers and physicians rarely know the chemical composition of the preparations they are administering . . . BRAN-type arsenic preparations, for example, contain trace metal contaminants, which may have biological effects.

This is partly true. But it is true for orthodox medicines as well, because users have to rely on the ingredients stated on the label, and if the quality control is not stringently maintained, there remains a possibility of adulteration. Thus, when a homeopathic drug labeled as Arsenicum Album-30 is procured from a well-known producer of homeopathic drugs, there is no problem for the researcher or the physician in knowing that this drug has only been derived from Arsenic trioxide in the proper procedure of homeopathic potentization. We did not examine whether Arsencum Album-30 used by us had any other trace metals, but we failed to detect the presence of arsenic by atomic absorption spectrophotometer in the Arsenicum Album-30 that we used.

Vehicle controls kept in glass vials contain the same dissolved solutes as noted above, but the levels may be lower because of a lack of vigorous agitation.

In our experiments, "vehicle controls" were also prepared by the drug producers in the same way (succussions) as the verum. But when administered to controls, they failed to elicit the kind of protective response we observed in the verum-fed group.

Glass vials manufactured by different processes using different starting materials leach different trace elements into solution. Thus, there may be differing levels of dissolved constituents in homeopathic and "vehicle" solutions if the vehicle is not agitated to the same degree as the homeopathic preparation.

This is the practice followed in homeopathic potentization process. Both verum and the placebo solutions are agitated in the same manner in the same type/batch of glass vials during preparation.

It is our firm belief that the study of homeopathy is more properly done by social and experimental psychologists and psychiatrists, in conjunction with medical doctors, rather than by experimental biologists.

If social and experimental psychologists and medical doctors are now interested in doing more studies on homeopathy, that is fine. But I do not agree that there is no role for experimental biologists to play when biological response to ultralow doses of homeopathy is an important unresolved area of research. After all, many important scientific discoveries have been made by nonmedical researchers even in the area of medical science. To find the truth behind this mystifying science, a concerted effort by all types of researchers should be welcomed.

One study was done to reproduce unpublished data from another laboratory that had reported significant efficacy in treating experimental cancer in mice using homeopathic preparations. Under the same reported laboratory conditions, opposite results were obtained. . . .

The issue of reproducibility became very controversial, particularly after 1988, after the famous article by Davenas et al[35] in *Nature* was reviewed by some people of different professions and the results could not be immediately reproduced. The initial result was later confirmed by another group of scientists in different laboratories located in different countries. But nonbelievers prefer to find the earlier nonreproducibility more convincing, rather than the reproducibility shown later. Such is the bias against homeopathy, despite the fact that the group of researchers confirming the initial results had the necessary expertise to conduct this kind of research. Incidentally, the types of research carried out in our laboratory, initially with cytogenetic protocols in mammalian model (mice) in vivo, and later using various widely accepted protocols from biochemistry through electron microscopy, have also not yet been replicated by others. In our laboratory, it often takes months if not years for our associates to develop expertise in handling so many state-of-the-art techniques. Furthermore, we work in an area of research that is always looked on with suspicion! Other researchers may not be attracted to the idea of treading in such dubious zones, by attempting to repeat our experiments and verify their results. However, in biological research, particularly when one uses mouse models, which have about 99% similarity with the human genome, there can be some variation depending on the individual research conditions and researchers (expertise) involved. Even so, similar trends in results should be obtained by all serious researchers if study protocols are followed correctly in attempts at replication. It is good that mainstream researchers are now attempting to replicate homeopathy research done in some other laboratories. Even though discrepancies in findings may arise, such repetitive research is very much welcome in the interest of knowing the truth behind this controversial science.

There is no harm in using these techniques to treat mild, non-life-threatening disorders. . . . Indeed, treating patients having a mild case of viral rhinitis with homeopathic remedies would be greatly preferable to frivolously prescribing antibiotics.

On the contrary, considering the entirety of the evidence from existing clinical and laboratory research, it can be stated that homeopathy may safely be used, and should be used as the principal mode of treatment, for all non-life-threatening disorders, because most orthodox medicines have adverse side effects whereas homeopathy has few, if any. For all life-threatening diseases, and in acute cases, the orthodox system should be adopted unhesitatingly. However, reports of studies showing benefits with homeopathy in critically ill patients with sepsis and patients with chronic obstructive pulmonary disease who are on ventilators are now available.[78] In both these instances, the use of homeopathy was integrated with standard critical care and shown to have benefit in addition to standard conventional critical care.

Rebuttal

It's true that the physicochemical nature of the homeopathic signal, information, memory, or imprint is not yet known. Therefore, I agree that much more research is necessary to throw light on the precise nature of this so-called homeopathic signal, which has been shown to exist by strong circumstantial evidence as well as from the results of many scientific experiments, a few of which have already been cited. The question of the nature of ligand binding of the homeopathic signal with special receptors on membranes is quite pertinent. However, the homeopathic signals may not behave as typical ligands (mostly known so far to be either polypeptide, steroid, or inorganic molecules) but can still possibly interact with some receptors (perhaps through ion-gated channels, which may be customized in the diseased state by conformational changes) in an unknown way to trigger a response pathway in the cytosol by the process of signal transduction. But again I admit that this is yet another challenging area that warrants vigorous research efforts in the future to arrive at a definite conclusion. There are, however, some other modes of signal transduction in which regulatory mechanisms of gene action can also be triggered (eg, by methylation/demethylation, alteration of form of DNA, and others). Some rapidly formed transient transcription factors (*jun, phos,* etc) are also known to be involved in expression of certain genes (eg, heat shock protein).

The regulation of gene expression in eukaryotes including human beings is still an incompletely understood subject. Much of the molecular nature of the regulatory network of gene expression is largely unknown. The nature and role of positional information, one of the features responsible for development of different tissues from different regions of the egg, are also very interesting questions in gene expression. Thus, gene expression is not always directly attributable to a DNA sequence.[73]

Many questions in different branches of science remain unanswered. The functions of many micro- and macromolecules are either not yet known or only partly known. Therefore, further research in homeopathy based on scientifically demonstrable facts

should be encouraged, because the mysteries behind many previously inexplicable observations have been brought to light only through sustained scientific inquiry.

Repeatability of results in well-conducted experiments is still a genuine concern in this field. But it may be achievable in the future dependent on the adoption of the exact experimental conditions and protocols. I hope this issue will also be resolved more convincingly with the participation of more researchers with open minds in this field of science, which until now has had only limited participation. Obviously more governmental involvement and funding for such research are also needed.

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