

Prover Susceptibility and the Ascending Dose: Did randomized, placebo-controlled trials disprove the homeopathic proving hypothesis?

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"The verifications of Hahnemann convince those who have intellectual integrity for scientific conviction, who will not sacrifice their intellectual integrity to the idols of the day, who will repeat Hahnemann's experimental verifications of his scientific observations and inductions as they should be repeated. Any other method than to take into the healthy body four drams of China twice a day to prove or to disprove the symptom similarity of China and intermittent fever is not a scientific experiment for the observation of Hahnemann."

-James Krauss, M.D., September 30, 1921, introduction to the Sixth edition of the Organon of Medicine; translated by William Boericke

Over the past decade, scientists and medical researchers have used sophisticated research methodologies in order to prove or disprove the efficacy of homeopathy. Based on their findings, editors of prestigious medical journals have concluded that there is no scientific validity to our therapeutic approach [1]. Given the high stakes of this research, the investigators' command of the homeopathic subject matter and the underlying assumptions reflected in these studies need to be carefully examined.

This is especially important in the pathogenetic trials whose stated objective is to investigate the validity of the claim that high potencies cause symptoms in healthy persons. While before 1994, the quality of pathogenetic trials was generally of "poor quality" [2], a number of more recent pathogenetic trials have applied the gold standard of scientific investigation - the randomized, placebo-controlled, double-blind trial. The authors of these studies imply that this approach could be used to scrutinize the central tenet of homeopathy - the "proving hypothesis."

Homeopathy is based on the discovery that a drug will cure if it can evoke symptoms similar to those of the disease. Therefore, to select the proper curative remedy, drug symptoms must be known. In 1776, Samuel C. Hahnemann, M.D. began to test medical drugs to determine the symptoms they could elicit. Over several decades of painstaking research, he perfected the homeopathic "law of proving" - the verifiable fact that all medicinal substances can cause symptoms specific to the substance. Hahnemann conducted most of his proving tests with diluted medicines (that is, the crude substances diluted in either water, alcohol or both). In the later years of his life, he advocated the use of substances potentized (diluted and succussed) beyond Avogadro's number, namely in the 30C potency.

Modern pathogenetic research presumes that the "proving hypothesis" is the notion that a drug can evoke symptoms in a high dilution (such as a 30C). This is erroneous. To test the "law of proving," i.e. to prove the claim that medicinal substances evoke symptoms in healthy persons, the trials should be conducted with crude substances (whether diluted or not). Testing remedies in high potencies does not examine this central tenet of homeopathy - it tests the effect of high potencies!

Moreover, in applying modern quantitative methodology to the testing of potentized remedies, these researchers have sacrificed several vital aspects of the original proving protocol that negatively affected the outcome of their investigations. They fail to take into consideration (a) the susceptibility of the provers and (b) the need to increase the dose systematically until symptoms develop. The prover susceptibility and the ascending dose are essential aspects of the homeopathic proving protocol, and without incorporating these, the conclusions of these trials are worthless.

Review of Premise and Results of Nine Pathogenetic Trials

For purposes of this review, I examined nine studies published in various academic journals between 1993 and the present time [3-11]. Of the trials examined, only two found substantial effects from high

potencies in randomly selected, healthy test subjects when compared with placebo. Seven out of nine studies found little or no effect [3-9].

A series of studies by Walach, et al. [3, 4, 6] addressed the question "whether in an HPT (homeopathic pathogenetic trial) a homeopathic substance, in an ultramolecular-potency as commonly used, would produce effects different from placebo and baseline fluctuations with a quantitative method." After three of these consecutive trials the author concluded, "this was clearly not the case." The Walach research teams never separated the ultramolecular hypothesis from the questions of provings. They stated their premise as follows: "The practice of homeopathy rest on symptoms, which have been produced by medicinal substances in healthy volunteers, often applied in ultra-molecular dilutions."

Vickers, et al. [7] in a "pilot study for a randomized, double-blind, placebo-controlled investigation of the proving hypothesis," claim that, "homeopaths should be able to distinguish a homeopathic medicine from placebo by taking both and observing their effects. If true, this would support an effect of homeopathic medicines different from placebo. If false, it casts serious doubt on the contemporary homeopathic knowledge base and on homeopathic pathogenetic trials (HPTs) as currently practiced." While acknowledging that for crude substances to cause symptoms in healthy people is "plausible," Vickers, et al. asserts that there is "no good evidence that [such ultramolecular dilutions] provoke symptoms in the healthy."

Vickers, et al. [8], in a separate study, set out to determine whether "homeopathically prepared mercury causes more symptoms (a 'drug proving') in healthy volunteers than placebo," using two control groups. No significant differences between the two groups were found. According to the authors, "the study failed to find evidence that mercury 12C causes significantly more symptoms in healthy volunteers than placebo." They concluded, "if proving symptoms exist, they are rare."

Brien, et al. [9] investigated whether "ultramolecular homeopathy has any clinical effects" using "the proving of homeopathic remedy Belladonna given in an ultramolecular-potency (30C), as model." The authors conclude that the study's data "have not provided evidence for the existence of a homeopathic effect using a commonly prescribed remedy." They, too, draw conclusions from these findings on the proving principles and on the concept of ultra-dilutions: "It could therefore be suggested that the central tenets of homeopathy are not valid, i.e. the concepts of provings and ultra-dilutions, which has considerable implications in terms of homeopathic practice."

Two more carefully designed trials did find positive evidence of proving effects. One by Möllinger, et al. [11] alleges that "little is known whether the symptoms produced by the remedy differ from symptoms produced by placebo." They tested two high-potency remedies and compared the results with placebo. They applied a flexible dosage method by repeating the remedies until symptoms appeared. The studies yielded "significantly more symptoms than placebo."

Walach, et al. [10] claims to investigate the proving hypothesis - the "pillar of homeopathy." They concluded that "homeopathic proving symptoms appear to be specific to the medicine," however, "rival hypotheses cannot be ruled out" because of small samples. The study also investigated whether any effects were due to "local" rather than "non-local" factors, following up on a hypothesis by Milgrom that ultramolecular effects could be explained in the context of the homeopath-patient relationship [12].

The Principles of Proving and Potentization

All of the nine trials share the premise that high potencies should bring out proving symptoms in healthy subjects. This premise is based on the fact that most modern provings make use of high potencies. However, the Hahnemannian law of proving does not stipulate the use of potentized substances. It simply states that every medicinal substance brings about specific signs and symptoms when tested on a healthy person (healthy being defined as "free from signs and symptoms of disease").

For the first three decades of his research, Hahnemann recorded the symptoms of medicinal substances from toxicological reports and from simple tests of the crude substances on himself and his volunteers [13]. Most Hahnemannian provings were made with more or less diluted crude substances. Eventually he noticed that high potencies brought out more symptoms in sensitive subjects than the crude dose and than even the lower potencies. The higher potencies yielded more subtle symptoms such as peculiar subjective sensations and mental changes that were valuable clinically for selecting the characteristic remedy for a disorder.

In order to bring out the full range of symptoms during provings, by the fifth edition of the Organon, Hahnemann recommended using the 30C potency, in a daily dose of 4-6 granules for several days (§128)[14, 15]. He chose the 30C potency precisely because he had found that, by experiment, at this level it evokes no primary or secondary symptoms or other side effects in most people. So it is far from surprising that the authors of the majority of studies cited did not find any statistically significant evidence of effect from high potencies when testing them on a random population.

In fact, the principles of "similars" and of "proving" exist independently of the "principle of potentization." The proving hypothesis is not dependent on the use of potentized substances. Crude substances may be used either homeopathically on the sick to treat disease, or on healthy persons to prove a remedy. The above trials are not tests of the proving hypothesis as claimed, but tests of the ultramolecular or ultra-high-potency hypothesis. The scientists' reasoning is this: Since homeopaths claim the proving principles also apply to high potencies, if the high potencies don't yield positive results, the validity of the homeopathic principles is called into question. This is erroneous reasoning. Why use substances whose properties are unknown or controversial to test something you could test using ordinary and known crude substances? Why test the homeopathic "law of proving" using "ultramolecular" substances rather than crude substances?

Ultramolecular (potentized) substances have been the main preoccupation of scientists investigating homeopathy because they do not see any "rational basis" for their use. In a review of studies [16], Walach, et al. blame homeopaths for their own preoccupation: "It is precisely homeopaths' emphasis on so-called high potencies (i.e., remedies succussed and diluted beyond Avogadro's number) that creates tension with modern science because no accepted rational theory exists that could explain increased therapeutic effect with decreasing amounts of the active agent, even to the point of there being no molecules of the initial agent present at all." Actually it is the researchers scrutinizing homeopathic concepts who overemphasize the ultramolecular substance.

So, when Walach, et al. [3] claim that "homeopathy lies on two principles: the law of similars and the potentization of homeopathic remedies," they were making a misleading statement. Homeopathy is the law of similars. Additionally, there is the law of potentization.

Interestingly, many scientist investigating homeopathy seem to prefer the terms "ultramolecular" and "ultra-diluted" to "potentized." In doing so they introduce a bias, implying implausibility. During the process of potentization, homeopathic pharmacists dilute the crude substance in a solvent, such as water, step by step, and agitate the mixture between each step. They may continue beyond the point when the last molecule of the substance has been diluted out (Avogadro's number). Scientists refer to this point and beyond as "ultramolecular dilutions." Terms like these emphasize the ultra-high degree of dilution, ignoring the function of agitation or "succussion." According to Hahnemann, the effect of the high-potency medicine lies in its high state of agitation, not in its level of dilution. The terms "potentization" or "dynamization" used by Hahnemann imply that their efficacy lies in the development of a force field that evokes a physiological effect even after the substance has been diluted out completely. Modern science has yet to confirm this hypothesis, though there is plenty of evidence in its favor, for example [see references 17, 18, 19, 20, 21].

Hahnemann's Proving Guidelines

For nearly 200 years, homeopathic medical scientists have painstakingly duplicated Hahnemann's drug testing protocols and repeatedly confirmed his observations. It was homeopaths that conducted the first double-blinded experimental study in the history of pharmacology, a proving trial conducted in Nürnberg, Germany in 1835 [22]. The above studies are an attempt to scrutinize 200 years of sound

scientific research. Are they reinventing the wheel? A closer look at Hahnemann's proving protocol shows modern trials to be sadly lacking.

While it is desirable to use a high-potency for provings, the Hahnemannian proving guidelines require that the proper dose necessary to induce symptoms be used. Susceptibility of provers to a substance depends on (a) the relative toxicity of the substance, (b) the size of the dose, and (c) the sensitivity of the provers. To put this into contemporary language, Hahnemann was fully aware of the dose-response relationship of toxic and potentized substances, and of the differing susceptibility of individuals.

In §121 of the sixth and final edition of the Organon of Medicine [23, 24], Hahnemann laid the theoretical foundations for successful proving experiments: "In proving medicines to test their effect on the healthy organism, one must bear in mind that strong, so-called heroic substances bring about alterations in health even in small doses, even on robust people; milder ones must be given in larger doses in these experiments; the weakest ones, on the other hand, reveal their true action only when tested on delicate, susceptible, and sensitive people who are free from disease" (3; § 121).

Hahnemann explained that some symptoms could only be elicited in persons with "idiosyncrasies." He points out that there are people who are basically healthy but "faint from the smell of roses and others who can become sick in many other ways, from eating mussels, crab, barbell, roe, from touching the leaves of some varieties of sumac, etc." (§117; a, b). Such sensitive people were to be used to bring out the symptoms of the weakest/most dilute of medicinal substances.

For example, in a case from my own practice [25], a patient had multiple food allergies, reacted violently to vegetable substances, and vomited every vegetable he ate. After taking repeated doses of *Bryonia alba* 30C (prepared from wild hops, a vegetable substance) for a cold, he developed severe symptoms of arthritis. He had red, swollen, stiff and aching joints, fever with intense thirst, scanty urine, and was just barely able to move. After learning of his peculiar susceptibility and recent doses of *Bryonia*, I offered him one whiff of spirits of *Camphor*, which antidotes the effects of all vegetable remedies [26], and by the end of the consultation his symptoms had disappeared and he was walking normally. Obviously, this individual had the necessary idiosyncrasy to become a prover for *Bryonia* 30C, and probably for many other vegetable substances in high-potency.

To illustrate the importance of sensitivity in choosing test subjects, I offer the following quotes from the sixth edition of the Organon:

- "Even a very moderate dose is often sufficient if the subject is sensitive enough..." (§130).
- "In this way the effect of an unknown medicine, even the mildest, will be revealed, especially if tested on sensitive subjects..." (§132).
- "If one takes pains to facilitate the investigation by choosing a truthful, sensitive subject..." (§137).
- "...the best will always be those that the healthy, unprejudiced, conscientious, sensitive physician undertakes on himself..." (§141).

Hahnemann also recommended that the dose be adjusted to make up for the difference in sensitivity. He suggested, "since one cannot know this in advance, it is highly advisable to start with a small dose of medicine for everybody and, where appropriate and necessary, increase it from day to day." He advised, "if only weak effects appear from such a dose, one can increase it daily by a few granules until the effects become clearer and stronger, and the changes in health are more perceptible." He concluded, "in that way the effect of an unknown medicine, even the mildest, will be revealed, especially if tested on sensitive subjects" (§ 132).

There is no indication that the investigators in any of the cited trials applied these proving guidelines, i.e. that they pre-tested provers for their (a) general sensitivity or for (b) any specific susceptibility to the (1) substance, (2) potency, or (3) dose in question, or advised their subjects to individualize and (c) gradually increase the dose until symptoms appeared.

Analysis of Trial Designs and Proving Protocols

In order to scrutinize the homeopathic proving hypothesis properly, a well-designed trial would have taken into consideration the entirety of the homeopathic proving guidelines and incorporated the full set of instructions to the minutest detail. It would have conducted the trials with sufficient doses of the remedies, selected only intelligent, conscientious, healthy, and above all, sensitive individuals, and tried several different medicines in the 30C potency to allow for general sensitivity and substance-specific differences in provers' susceptibility, and would have required that doses be increased until symptoms develop.

The researchers of all trials under review with negative results chose to ignore in their trial design the dose-susceptibility relationship. They randomly selected "provers" without regard to their sensitivity, and gave all of them the same dose. Clearly, they did not even examine the Hahnemannian proving protocols. They did not pay attention to the recommendations designed to evoke symptoms from high potencies. While the methodologies used could possibly find some efficacy if one were to engage in a mere "symptom gathering exercise," in a trial expressly aimed at scrutinizing the conceptual foundation of homeopathy, the approach amounts to a significant error of omission.

Some of the authors of the cited studies mentioned the factors of prover sensitivity and dose. However, they failed to incorporate these factors in their study design. Vickers, et al. [7] commented on the rationale of testing the proving hypothesis by using a crude substance as "plausible," yet they wrongly inferred from their own negative results that this challenges the "proving hypothesis." They, too, failed to differentiate the proving principle from the ultra-high-potency principle.

In a separate study by Vickers, et al. [8], they also mention prover susceptibility: "Homeopathic practitioners claim that to respond to a drug proving, a subject must be sensitive to the medication being tested (Vithoukias, 1998), an idea analogous to that of finding the individual medication most suited to the patient" (see also [27]). While claiming that there is disagreement about the percentage of a population likely to be sensitive to the medication, they quote between 1% and 95% and concede that the absence of evidence in the study "should not be over-interpreted as absence of the proving phenomenon." Yet, in their abstract, the same authors erroneously conclude that, "if drug-proving phenomena exist, they appear to be rare."

When a research team incorporated even a portion of one of these factors [11], they obtained positive results. This is the only one of the nine trials that applied a flexible dosage method by repeating the remedies until symptoms appeared. But this is not the ascending dose method Hahnemann had recommended. While this trial showed positive results, one could not expect this method to consistently evoke symptoms in randomly selected subjects. Most "robust" subjects without "idiosyncrasies" would never get symptoms, because they would need a dose that is specific to their relatively lower susceptibility.

Walach, et al. [6] did mention the factor of dose. "Another point in question is dosage: Hahnemann, and indeed, modern HPTs, use a flexible dosage scheme, with dosage applied until symptoms start emerging. We decided to use a fixed and rather weak dosage scheme, because we wanted to avoid possible overdosing. Instead, we used a remedy with broad application and presumably broad susceptibility, so as to enhance the number of possible responsive subjects."

This clearly indicates that some researchers were aware of the need to individualize the dose. Yet they falsely claim that Hahnemann's dosage protocol requires a repetition of the same dose, rather than an increasing dose, until symptoms appear. The scientists' claim that they used a fixed duration of a dose "to avoid overdosing" is very interesting considering the flexible method is designed to avoid overdosing, and the danger of overdosing is much greater in using the same dose for a fixed duration because the more sensitive subject may not need a dose for the full duration. According to protocol, you give a sufficient dose to bring out symptoms, then you stop. This avoids overdosing.

Discussion

Hahnemann took the issue of dose very seriously. In addition to his dosage recommendations for proving experiments, he also left detailed instructions on the individualization of the dose when treating sensitive patients. He pointed out that some patients needed considerably smaller doses, and

recommended using the olfactory dose, or, if necessary, additional dilutions of a given potency, should proving symptoms appear in these sensitive patients (§ 248).

Some researchers drew conclusions about the relative number of persons that “prove” a remedy. Goodyear, et al. [5] state that “only a small percentage of individuals actively prove; Walach estimates that 1% of individuals proved in his study while we have suggested that between 10 and 20% are likely to prove.” This flawed expectation is apparently based on the results of previous trials and their common failure to incorporate selection criteria for prover susceptibility and the “ascending dose” method. At least in theory, all healthy persons prove highly active substances in high-potency, provided they are sensitive, and provided they take the remedy in a dose adequate for their individual susceptibility.

We can deduce from standard homeopathic theory that an average dose of a high-potency can be expected to bring out symptoms in an average number of provers in a select, susceptible population. That same dose will predictably yield smaller than average results when tried on the general (random) population. This means, in a randomized, placebo-controlled study, the difference between placebo and verum would likely be weak to insignificant. This is exactly what the researchers found, thus proving the homeopathic theory to be correct!

It is noteworthy that several of the above trials were conducted with significant cooperation from homeopaths and homeopathic students who should be familiar with individualization of dose according to sensitivity of the proving subjects. Many otherwise knowledgeable homeopaths who conduct proving experiments apparently still do not make the distinction between potency and dose. One reason for this may be a historical event: the tragic delay in the publication of the sixth edition of the *Organon*.

When the sixth edition was finally published in German in 1920, nearly 80 years after Dr. Hahnemann’s death, many homeopaths still did not realize that he had made a clear distinction between potency and dose. Mathias Dorsci, Georg von Keller and Gerhard Koehler were some of the first modern day homeopaths to point out the distinction [28, 30, 31]. By 1921 when the English translation first appeared, many homeopaths had already become accustomed to reducing the dose by increasing the potency, basing this practice on James Tyler Kent’s interpretation. Kent maintained that higher and higher potencies should be used to reduce the dose of the remedy to the “minimum dose” [29].

Hahnemann had made a distinction between a low dose and a high-potency in the fifth edition [14, 15]. He explained it even more clearly in the sixth edition [23, 24]: In §275 he states that when a medicine is homeopathic to the disease, it is harmful in too high a dose. In §276 he adds, “the higher its potency the more harm it does,” and “if the dose is appropriately small, a well-dynamized medicine becomes increasingly curative” (§277). Thus, Hahnemann taught to reduce the risk of harm by diminishing the amount given (by diluting the dose) not by increasing its dynamization or potency, as Kent incorrectly claimed. In the subsequent paragraphs, Hahnemann explains that the appropriate dose depended on the individual sensitivity of a patient and can only be determined by pure experimentation on each individual patient.

To prevent further harm during treatment, Hahnemann developed a new potentization method: He increased the steps of dilution from 100 to 50,000, thus reducing the risk of harm from the lower potencies (§270). However, when the sixth edition of finally appeared, homeopaths mistook the new technique of these Q-potencies (quinquagintamillesimal, also improperly called LM-potencies) for the mere “plussing” (a small increase in potency) of a C-potency remedy [30, 32] and ignored it.

The distinction between potency and dose and its individualization during treatment or proving has not yet found its way into all homeopathic educational institutions. Some homeopaths appear to be either unaware of the distinction or ignore it in their practices. Even a recently published web-based set of guidelines titled *ECCH Recommended Guidelines for Good Provings by the European Council for Classical Homeopathy* contains no reference to Hahnemann’s individualization requirements in selecting provers. There is also no mention of the Hahnemannian controls – the ascending dose to accommodate for the individual susceptibility of provers (*Organon*, §132).

The revelations on the researchers' failure to incorporate Hahnemannian controls in their pathogenetic trials by no means exonerate current provings or much of the modern homeopathic database from the accusation of questionable validity. On the contrary - the latter themselves deviate from the Hahnemannian standards. I therefore join Vickers, et al. [7] in the question of what this means for the reliability and completeness of modern-day homeopathic provings.

Modern scrutiny of pathogenetic research has been largely futile because, by definition, randomization methods do not screen for individual susceptibility, and, without the increasing dose method, the wide range of susceptibility among a random population cannot be addressed. Had the scientists used a lower potency that contains molecules of the substance, the studies may have been appropriate for random populations and yielded better results. But then they obviously could not have been used to test the "high-potency hypothesis!"

Unfortunately, errors of omission have led to false trial results that have dire cumulative consequences. ESM de Lange de-Klerk, in his commentary on one of the trials in the journal *Focus on Alternative and Complementary Therapies*, summarized the results of the study with the statement, "there is no evidence that potentized Bryonia was different from placebo" [33]. The headline in the same issue for a review of the second trial read, "symptoms produced from homeopathic Belladonna 30CH are likely due to chance" [33]. The reviewers deemed both studies "carefully conducted." Given that most of the trials found no efficacy for "ultramolecular" pathogenetic effects, supposedly "the pillar of homeopathy," it is no surprise that scientists around the world have concluded that homeopathy is simply a placebo effect.

Conclusion

In the nine trials examined, researchers failed to find evidence for the homeopathic proving hypothesis because they started with the wrong premise: They confused the proving hypothesis with the efficacy of high potencies. They botched their attempts to scrutinize high-potency provings because they failed to incorporate conditions and controls that are an inherent part of homeopathic provings. Such errors have consequences.

With only two out of nine trials finding evidence of a "proving effect," the casual observer is left with the impression that ultra-high potencies are suspect, and that the proving hypothesis, and thus all of homeopathy, is a myth. It is not surprising that many scientists have concluded that there is no rational basis for homeopathy. Researchers have accomplished this impression by deviating from the original Hahnemannian proving protocols and further aided it by a confusion of concepts and terminology that serves to obscure these errors of fact and omission.

Though the negative results of the studies under review actually proved the correctness of the homeopathic proving theory, unfortunately their authors seem unaware of this fact. There is no indication anyone outside the homeopathic community has taken notice. The significance of the errors in these trials extends beyond the problem of proving accuracy and the impact it unquestionably has on future studies. Improperly designed studies yielding false negatives due to inadequate or incomplete understanding or application of homeopathic theory have a devastating effect on the scientific community's perception of homeopathy that will be difficult to reverse. And, unless the errors are exposed, they will reverberate into future policy guidelines drawn by governments and regulatory bodies.

In summary, while the trials' formal quantitative methodology was of above-average quality, they fell short on substance. We have entered an era when the sophistication of the methodology used in investigating alternative systems of medicine is sometimes greater than the investigator's grasp of the subject matter they set out to examine. It is unfortunate that nine inadequate trial designs may have contributed to a rejection of the homeopathic healing system for all the wrong reasons.

"Don't try to establish an understanding with the world of conventional medicine. They will suck out the good and leave the meaningless. And then they will call the shell that is left 'homeopathy,' and others will have to dig again for the truth."

--- Julian Winston, American Homeopath, 2005. p. 11

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