

# **EVIDENCE-BASED VETERINARY HOMEOPATHY**

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### **PREFACE**

This lecture was conceived out of two complementary needs. I have always harbored an interest in the science behind homeopathy: explanations for what make those little white pellets perform such miraculous actions on the body. And I have observed that veterinarians who practice homeopathy are rightfully consumed with clinical matters, namely how to become better prescribers to increase success rates, to the exclusion of time to review literature on the science of homeopathy. Meanwhile, the demand to prove the “scientific” nature of homeopathy is increasing. As denialists find their way into regulatory boards, either by direct membership or by influence, falsehoods about the lack of studies in homeopathy are easily perpetuated. Yet veterinarians who practice homeopathy are largely ignorant of the wealth of studies that refute such claims.

It was only logical that I embark upon a project to collate the relevant studies out there. In my travels through PubMed and other sites, while searching with such words as “meta-analysis” and “bias,” I came across numerous studies, published in mainstream conventional journals, that cast doubt upon the entire publication process and trustworthiness of “evidence.” Since the point of this paper is to focus on homeopathy, I have merely introduced some of these other papers in an effort to put the whole “evidence based medicine” concept in perspective.

One of my goals is to provide my colleagues with material to present at other meetings. I encourage you to lift as much from this paper as you need to. Along those lines, in lecturing on the evidence in the past, I have found that it is crucial to make sure the audience has a basic understanding of homeopathy so that the unique considerations, especially in clinical trials, can be understood. Accordingly, I have included lecture notes in the first section below that are purely for your use should you choose to lecture on the topic in the future. This first portion focuses on homeopathy: what it is, how it is applied in practice (the nuts and bolts), basic principles, the remedies (how they are prepared, sources, administration), and indications. The second part focuses on the “evidence” supporting homeopathy, particularly the ultramolecular doses, provings, and clinical efficacy.

The notes below on the evidence in homeopathy are highly incomplete, and intended to highlight some of the more important and interesting studies only. Where applicable, resources are provided that contain more thorough lists and/or reviews of the research.

### **INTRODUCTION**

Since its founding as an empirically-derived system of medicine in the late 19<sup>th</sup> Century, homeopathy has suffered from an extreme lack of respect among practitioners of conventional medicine. The founder of homeopathy, Samuel Hahnemann (1755-1843), based his theories of practice on meticulously documented experimentation and

observation, and initiated the first system of drug-testing. Unfortunately for him and for homeopathy, Hahnemann was no diplomat, and the medical method he founded was markedly less interventional and expensive than the prevailing treatments of the time, (blood-letting, leeches, mercury, etc.). His disparaging writings about these mainstream treatments had the net effect of a negative response toward his new system of medicine by the “regular” medical community.

Three years after the American Institute of Homeopathy was founded in 1844, the American Medical Association was founded in reaction. A clause in their charter prevented members from consulting with practitioners “whose practice is based on an exclusive dogma, to the rejection of the accumulated experience of the profession.”<sup>i</sup> Allopathic doctors risked expulsion from the society if they talked to homeopaths. This clause remained in medical society applications until the 1920’s.<sup>ii</sup>

Homeopathy has suffered the lingering effect of the poor relationship between the homeopaths and the allopaths. Although it was the first system of medicine to stress experimentation at a time when unfounded ideas about the origin of disease abounded, over time the scientific method evolved into the doctrine of clinical trials and a hierarchy of evidence, leaving almost 200 years of documented case reports and pathogenetic trials to be relegated to the oblivion of scientific credibility.

This presentation is an attempt to dispel unfounded notions about the voodoo nature of homeopathy. We will explore the basic principles and practice of homeopathy, and review the scientific literature that relates to each topic.

## THE PRINCIPLES OF HOMEOPATHY

Homeopathy is based on a set of principles:

1. *Similia similibus curentur*, or “let like cure like”
2. Drug provings or pathogenetic trials
3. The minimum dose
4. Dynamization or potentization of remedies
5. The single remedy
6. Theory of chronic disease

The *similia* principle is the basis of homeopathy. All remedies are prescribed based on their resemblance of the condition in the sick patient to the symptoms documented for the remedies when given to the healthy human test subjects, known as provers, during pathogenetic trials, or provings. For example, in the proving of arsenicum album, a remedy derived from arsenic, the provers reported frequent thirst, nausea, vomiting of blood, diarrhea, restlessness with severe weakness- and all symptoms worse after midnight.<sup>iii</sup> Likewise, when a dog wakes its owners up at 1:00AM with an urgency to go outside, and diarrhea and vomiting commence with the dog pacing around all night, wanting to drink water (but the owners removing the water bowl for fear that this will promote more vomiting), then the remedy that will help this dog is arsenicum album.

The provings, or pathogenetic trials as they are described in the literature today, were Hahnemann’s answer to the wealth of unfounded theories in his time. He conducted his experiments on healthy humans of both sexes and all “constitutions.” The individuals

were given small doses of a substance and asked to record the symptoms that ensued. These symptoms would be on the mental/emotional and physical levels. Of highest importance were the modalities, or what made the symptoms better or worse. For example, the prover might feel better elevating a throbbing leg, or applying cold compresses to it, or taking a brisk walk on it. When all the provers have recorded all of their symptoms, the symptoms are collated, commonalities are found, and a hierarchy is usually revealed emphasizing the most frequently reported symptoms and modalities, along with any strange/rare/peculiar symptoms and sensations. These symptoms then comprise the *materia medica* for that remedy.

Conversely, when a homeopath takes a case, s/he then consults a *repertory*, which is a list of all symptoms with their corresponding remedies. Repertories are divided into sections, (mind, the different body parts, generalities, etc.), and these sections list the symptoms alphabetically. The symptoms, as they appear in the repertory, are known as *rubrics*. Rubrics can have subrubrics. For example, “Cough; Air; Dry; cold” would be a rubric for a cough that is worse in dry cold air. In the Complete Repertory, 11 remedies are listed under this subrubric.

When Hahnemann began his experiments with homeopathy, he administered small doses of the substances that were indicated. He found that patients initially underwent an aggravation, followed by an amelioration. For example, a patient given a small dose of arsenic for a gastrointestinal disorder might initially respond by more vomiting and diarrhea, followed by recovery. Hahnemann circumvented this by giving smaller and smaller doses, actually diluting the material, and finding the aggravations were diminished. He concluded that the smallest dose indicated should be given to the patient (the “minimum dose”) to prevent such aggravations.

In making these dilutions, Hahnemann rigorously pounded the solution on a leather-bound book. His thinking was to evenly distribute the material throughout the solution. This evolved into the process of dynamization, or potentization. Although it is questionable as to whether or not Hahnemann was aware of Avogadro’s number<sup>1</sup>, the reciprocal of which marks that point at which a dilution would contain no material substance, Hahnemann proceeded with administering dilutions of remedies that exceeded the reciprocal of this “critical” number and found that the effects persisted while the aggravations did not. During the process of potentization, a substance is diluted initially in alcohol, and then in water. (Certain dry substances, like minerals, for example, are first “trituated,” or ground on milk sugar and diluted for the first few dilutions using this milk sugar.) At each successive dilution in the liquid, the container is shaken, or “succussed.” Dilutions are made on one of three scales: X or decimal are 1:9 dilutions; C or centesimal are 1:99; and Q or LM are 1:50,000. The nomenclature is such that a 200c potency of a substance would indicate that it has been diluted 1:100 200 times, with succussions between each dilution.

The provings brought out a host of useful information. Since each remedy was able to produce a variety of symptoms in the provers, and each remedy produced symptoms unique to itself, Hahnemann found the need for polypharmacy became obsolete. One

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<sup>1</sup> In 1811, Amedeo Avogadro proposed the concept that would later be named after him. It was not until 1865 that Johann Josef Loschmidt assigned a value to this number,  $6.02 \times 10^{23}$ .

remedy was capable of curing the full set of symptoms produced in the sick patient. These symptoms are placed in different categories, and include:

1. General symptoms: those affecting the whole patient, like worse in rainy weather or burning pains or aggravated by exertion.
2. Particular symptoms: those affecting a specific location on the patient, like blisters on the ear or swelling in the lower limbs.
3. Concomitants: symptoms that occur at the same time as the main complaint. For example, a skin eruption that occurs during a fever, or back pain that occurs with the flu.
4. Alternating symptoms: symptoms that alternate in their appearances, like otitis externa alternating with seizures.
5. Modalities: what makes a complaint better or worse. This could be elevating the affected leg, applying cold compresses to it, or applying pressure to it. It could also be that the leg is worse every day at 11AM or in hot dry weather. Modalities are very important in distinguishing one remedy from another.
6. Characteristic symptoms: what is characteristic about the problem in *this* patient, versus in other patients with the same complaint. For example, one dog with kennel cough might be extremely lethargic, while another might vomit (as opposed to just gag) at the end of each coughing spell.
7. Strange/rare/peculiar: what is unexpected. For example, appetite increased with vomiting, or a headache ameliorated by light.
8. Mental/emotional symptoms: These include the disposition of the sick patient. For example, one cat with diarrhea might be very clingy, while another might be very nervous/anxious and fruitlessly pacing. The mental/emotional symptoms are most significant when they are changed from the patient's well state.
9. Physical symptoms: the specific physical symptoms of the patient, including such details as the color, texture, and odor of the diarrhea, for example.
10. Sensations: not relevant in veterinary medicine, but very helpful in human homeopathy.

Finally, Hahnemann was responsible for delineating the theory of chronic disease. He found that symptoms produced by the patient, even when originating from totally different organ systems, were all part of that patient's "chronic disease." By giving a different remedy to extinguish each symptom as it arose, he found that he was only putting out fires. But when he considered the entire symptom complex of the patient- in other words, all the problems the patient had over the year(s)- he was able to find one remedy that would make this patient healthier and rid him/her of the tendency to produce *all* of these problems.

Along these lines, homeopaths are cognizant of three courses for a disease: palliation, suppression, and cure. The goal of a successful homeopathic prescription is to cure- to rid the patient of all symptoms permanently, without the need for further medicating, and while increasing the patient's overall well-being. When palliation occurs, the patient's symptoms may disappear temporarily, but return in due time, sometimes with even more force. (Think otitis externa in Golden Retrievers.) When suppression occurs, the symptom disappears, but "deeper" more serious symptoms will replace it. This is the case

with excision of a tumor that is followed by metastasis, or by hiding and inappetance in cat being medicated for chronic vomiting.

## ACTIVITY BEYOND THE RECIPROCAL OF AVOGADRO'S NUMBER

Most of the “sticking points” for non-homeopaths center around the idea of activity in dilutions beyond the reciprocal of Avogadro's number (BRAN) ( $6.022 \times 10^{-23}$ ), the point at which no material substance is expected to be found in a solution. These highly diluted solutions are also known as “ultramolecular dilutions.” This concept is contrary to prevailing pharmacologic principles which link the efficacy of a bioactive agent to its activity as an agonist or antagonist at specific receptors, or its ability to block or enhance specific enzyme, channel, transduction or transport systems.<sup>iv</sup> It needs to be emphasized at this point that one can practice homeopathy and *never* utilize a potency that exceeds the reciprocal of Avogadro's number. In other words, while the concentrations of the substance are small, some of the original material, albeit in a small amount, can still remain. In fact, one can practice homeopathy using tinctures of herbs (when such substances are indicated as the *simillimum*), but might run the risk of severe aggravations.

A variety of experiments in physics and chemistry have demonstrated activity in water prepared according to homeopathic method (dilution and succussion) including for ultramolecular dilutions. Space and time are too limited to publish a review of all relevant studies. The reader is referred to the HomBRex website for current updates: (<http://www.carstens-stiftung.org/>); and to Martin Chaplin's website, “Water Structure and Science”: <http://www1.lsbu.ac.uk/water/index2.html>, which constantly updates information on water and contains sections specifically relevant to homeopathy.

Thermoluminescence is a phenomenon whose application to the study of the structure of solids has been fully developed. It has been used to study the structural changes in water that occur when lithium chloride or sodium chloride are prepared in it via successive dilutions to the hundredths, each dilution undergoing vigorous mechanical stirring, until the 15<sup>th</sup> dilution is reached ( $15c$  or  $10^{-30} \text{ g cm}^{-3}$ ). In short, each solution is frozen to  $-20^\circ\text{C}$  ( $-4^\circ\text{F}$ ) to achieve stability in its crystallization pattern, then immersed into liquid nitrogen and kept at  $-196^\circ\text{C}$  ( $-321^\circ\text{F}$ ) for 24 hours. The solutions are then irradiated and placed back in liquid nitrogen for an additional week. Finally, they are placed in thermoluminescence equipment and their respective glows recorded while being rewarmed. The results showed that the thermoluminescence glows of the three systems were substantially different. Moreover, the findings were reproducible in the course of many different identical experiments and independently verified.<sup>v,vi</sup>

Rey hypothesizes that “this phenomenon results from a marked structural change in the hydrogen bond network initiated at the onset by the presence of the dissolved ions and maintained in the course of the dilution process, probably thanks to the successive vigorous mechanical stirrings.”<sup>vii</sup>

Using electron microscopy and atomic force microscopy, researchers found that substances sequentially diluted in double-distilled water at least six times and then shaken in-between will create water clusters or ice crystals (“I<sub>E</sub> crystals”) that maintain an electrical field and that do not melt in room temperature water. These crystals have a unique geometric shape as well as charge and density.<sup>viii</sup> Research conducted by 10

different professors in varying scientific fields have tested the biological effects of these I<sub>E</sub> crystals and have found remarkable effects. Benjamin Bonavida, PhD., professor and former head of UCLA's department of immunology and microbiology, found a two- to a hundred-fold increase in cytokines (mediators of immune function that protect against infection and tumor growth). Selim Senkan, PhD., head of UCLA's department of chemical engineering, found that I<sub>E</sub> crystals placed as a gas fuel additive reduce carbon deposits on engine piston tops. Various auto emissions have also been reduced from the I<sub>E</sub> crystals.<sup>ix</sup>

NMR studies on ultramolecular dilutions prepared according to homeopathic techniques show varying results depending on the particular measurements studied. In a recent study measuring High-field 1H(1) and T(2) NMR relaxation time measurements of water prepared with quartz (10c-30c), sulfur (13x-30x), and copper sulfate (11c-30c), compared to controls, no changes were found at 500 MHz; but one year after preparation, T(1) relaxation times for homeopathic sulfur were increased with statistical significance compared to controls.<sup>x</sup>

Demangeat measured 20-MHz R1 and R2 water proton NMR relaxation rates in ultrahigh dilutions (range  $5.43 \cdot 10^{-8}M$  to  $5.43 \cdot 10^{-48}M$ ) of histamine in water and in saline, prepared as centesimal dilutions with vigorous agitation in controlled atmospheric conditions. He found a significant difference between histamine solutions and controls (solvents) which disappeared after heating the samples. Interestingly, overheating of homeopathic remedies, as can occur if left in a car on a summer day, are known to deactivate the remedies. Demangeat attributes the difference in histamine solution from controls to a more organized state of water in the unheated samples. He discusses the possibility that stable supramolecular structures, involving nanobubbles of atmospheric gases and highly ordered water around them, were generated during the vigorous mechanical agitation step of the preparation, and destroyed after heating. Since the histamine solutions remained distinguishable from solvents up to ultrahigh levels of dilution (beyond  $10^{-20}$ ), he suggests that the histamine molecules might act as nucleation centers, amplifying the phenomenon which was detected at high dilution levels.<sup>xi</sup>

A recent paper focused on the role of glass-derived silicates in water and the role that these might play in very dilute solutions. Aqueous serially succussed and diluted (SSD) preparations using either L-glutamate or acetylthiocholine in purified and deionized water in either borosilicate or soda-lime glass tubes or polypropylene tubes versus deionized water alone were tested for their ability to affect enzyme stability (acetylcholine esterase). Enzyme assays demonstrated that enzyme stability in purified and deionized water was enhanced in SSD solutions that were prepared in glass containers, but not those prepared in plastic. The silicates were present in concentrations too low to have direct *in vivo* effects.<sup>xii</sup> While the silicates may affect the results of *in vitro* studies using ultramolecular dilutions, it is also possible that they may have a stabilizing effect on other substances prepared as homeopathic remedies. Dissolved silica is capable of forming solid particles with complementary structures to dissolved solutes and macromolecules (that is, imprints), and such particles will “remember” these complementary structures essentially forever.<sup>xiii</sup>

Elia's group at the University of Naples has published many papers (in a variety of journals ranging from *Journal of Thermal Analysis and Calorimetry* to *Homeopathy*) showing their findings of physico-chemical properties of extremely diluted solutions

(EDS) prepared with succussion. Using well-established techniques such as flux calorimetry, conductometry, and pHmetry, they found differences in the EDS in physico-chemical parameters, even taking into account the chemical impurities from the glass containers. In fact, some physico-chemical parameters evolved with time. They interpreted their findings on the basis of the thermodynamics of dissipative structures, described by Nobel Laureate Ilya Prigogine. Dissipative structures are complex, self-organizing systems, far from thermodynamic equilibrium. Within a dissipative structure there is long-range interaction between particles, and they exchange energy and matter with their environment. Examples include cyclones, hurricanes, and lasers.<sup>xiv,xv</sup>

A paper from the Materials Research Institute of Pennsylvania State University (PSU) discusses the “wide range of disparate observations on water (and other liquids which share one or more structural or bonding parameters) to support the case that water can indeed have its properties and hence its structure changed rather easily in non-linear ways without any change of composition.” In other words, it is the properties that arise out of the structural changes which can occur “more easily and dramatically than chemistry changes [the properties],” that may account for the transfer of information from the material substance to the water in the process of dilution and succussion.<sup>xvi</sup>

The PSU paper also supports the role of epitaxy, the transfer of information, not material, from the surface of one material, usually solid, to another, usually liquid. Citing Rey (above) and other research, it concludes:

This data again supports the case that extreme dilution + epitaxy + succussing, can plausibly result in a water with different structures, possibly containing a permanent nanobubble colloid, and it can have measurably different physical properties, a very plausible result from the viewpoint of materials science, and consistent with the extensive data from the homeopathy research.

The argument that material substance must somehow be present in the dilutions has been revisited by Chikramane *et al.* Using three physico-chemical techniques and 30c and 200c potencies of remedies purchased at the market, they were able to demonstrate the presence of the starting metal in the solutions of either Aurum metallicum, Cuprum metallicum, Stannum metallicum, Zincum metallicum, Argentum metallicum, or Platinum metallicum. The quantities of the metals were relatively consistent between potencies and were found in the picogram range, but did vary from batch to batch and from one manufacturer to the other. The authors attribute the presence of the metal nanoparticles to their adsorption to the surface of nanobubbles and cavitations that form during the process of succussion which generates ultrasound waves.<sup>xvii</sup>

The above studies demonstrate activity of potentized substances in water/alcohol, but do not account for the transfer of some sort of molecular signal via sucrose or lactose pellets, the common method of dispensing homeopathic remedies. Maity *et al* have conducted a series of experiments testing the concept of dielectric dispersion on lactose pellets soaked in two different homeopathic remedies (sulphur or cuprum) at three different potencies (30c, 200c, 1m). Multiple resonance frequencies known as “frequency sets” were detected for each remedy at each frequency, which is characteristic for three-dimensional structures; and these frequency sets were different from that of the plain lactose pellets. These results were observed repeatedly. The researchers conclude that this technique may be useful in identifying homeopathic medicines.<sup>xviii</sup>

The preponderance of evidence in physicochemistry supports activity in ultramolecular dilutions that have undergone processes akin to succussion. The exact mechanism(s) by which water carries “information” from the original substance is still being investigated, with a variety of plausible theories available. In summary, specific clinical effects may be conferred by remaining material on surfaces, aerosol material reintroduced, bacterial material introduced, imprinted silicates, and remaining particle clusters. Non-specific clinical effects may be derived from silicates, dissolved and particular; nanobubbles and their material surfaces; redox molecules produced from water; natural water clustering; stabilized water clustering; ions, including from glassware; and ethanol solution complexity.<sup>xix</sup>

Obviously, for the medically-minded healers, the physics and chemistry of ultramolecular dilutions can make our heads spin while bordering on the clinically irrelevant- and the clinics are where our interests lie. In the next section, we'll explore some of the more interesting studies performed in living systems.

### ***IN VITRO* AND *IN VIVO* BIOLOGICAL STUDIES USING ULTRAMOLECULAR SERIALLY AGITATED SOLUTIONS**

Witt *et al* performed a systematic review of 67 *in vitro* experiments gleaned from 75 journals. All studies involved stepwise agitated dilutions with substances in  $>10^{-23}$  concentrations. Thirty-three percent were replications. Quality was assessed by the modified SAPEH score<sup>2</sup>. Seventy-three percent showed an effect with ultramolecular

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<sup>2</sup> Score for Assessment of Physical Experiments on Homeopathy. SAPEH had been developed to assess the quality of physical research in homeopathy. [Becker-Witt C, Weißhuhn TER, Lüdtker R, Willich SN. Quality assessment of physical research in homeopathy. *J Alt Compl Med* 2003;9:113-32.] It is based on three quality constructs - methodology, experiment standardization, presentation - that divide into 8 items, checking for 10 criteria. Each item scores 1 point for an affirmative answer, except controls and experiment standardization with 2 points each.

The methodology items check that the experimental design uses techniques to control factors that may cause bias (e.g. systematic or random errors). Mentioning controls scores 1 point that is subtracted again if their nature allows for chemical differences to the potencies. Identical composition is assumed if controls have undergone a similar contaminant-affecting preparation (succussion or potentizing) as the test potencies. It would earn 2 controls points, accepted are all meaningful descriptions such as "produced like the verum" or "succussed (shaken, vortexed, sonicated, ... ) medium." Further methodology items cover blinding (preventing handling differences and bias effects), randomization (to prevent systematic errors), consistency (internal replications, ensuring test system stability), and the use of statistics. Experiment standardization was adapted to the *in vitro* field, instead of the somewhat unspecific original criteria 'external factors' and 'experimental setup' that can affect results, the item now checks for the use of a buffer or buffered medium, and for standardized temperature and incubation



dilutions, including 68% of 18 studies showing a SAPEH score  $\geq 6$ . The experiment types consisted of :

- indirect healthy cells (37%)
- direct cell-free systems (27%)
- indirect pathological cells (19%)
- direct healthy cells (10%)
- pathological donors (8%).

Cells studies consisted of:

- basophils (42%)
- non-cellular systems (27%)
- cultured cells (19%)
- others: lymphocytes (6%), erythrocytes (3%), neutrophils (3%).

The authors concluded that even experiments with a high methodological standard could demonstrate an effect of high potencies. No positive result was stable enough to be reproduced by all investigators. The authors recommend a general adoption of succeeded controls, randomization, and blinding to strengthen the evidence of future experiments.<sup>xx</sup>

Basophils were the cell type overwhelmingly represented in these studies. Effects of SSD on basophils have been studied for over 25 years. One of the earliest and most famous studies was published in the journal *Nature* by the late Nobel nominee Jacques Benveniste *et al.* Using substances which are known to have a stimulatory effect on human basophils at ponderal doses, Benveniste, in collaboration with four other laboratories, demonstrated that the basophils are sensitive to infinitesimal doses of these substances: anti-IgE antibodies, calcium ionophores, and phospholipase A2, for example. Other ultra-diluted substances, such as anti-IgG antibodies, known to have different biochemical specificity on the membranes, demonstrated a lack of effect on the basophils. The dose-response effect showed alternating peaks and inactivity troughs up to very high dilutions corresponding to practically zero antibody concentrations. Vigorous succussion (10 seconds with a vortex) were required to obtain maximum activity at the infinitesimal dilutions. The stimulatory effect persisted even after ultrafiltration through membranes which should have retained the antibody out of solution.<sup>xxi</sup>

A pseudo-scientific highly politicized affair arose from these studies, and it was not until 2004 that an independent triple-blinded study confirmed these findings. In the original Benveniste studies, basophil *activation* by substances in dilution was performed. In the 2004 studies, *inhibition* of basophil degranulation by SSD substances was performed. In order to demonstrate that high dilutions of histamine were able to inhibit

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time. The remaining communication about the experiment is covered by presentation of objectives and results, which have to be reasonably detailed and understandable. The modified SAPEH should be read at item level to assess an experiment. The total SAPEH score and its subscores support only rough global impressions and should always be accompanied by score details. For the purposes of the present study, 6 or 7 points with controls of equal contamination would indicate a reasonable control for bias, and  $>7$  points including 2 for controls) would strengthen this.

basophil activation in a reproducible fashion, several techniques were used in different research laboratories. The aim of the study was to investigate the action of histamine dilutions on basophil activation. Basophil activation was assessed by alcian blue staining, measurement of histamine release, and CD63 expression. Study 1 used a blinded multi-centre approach in four centers. Study 2, related to the confirmation of the multi-center study by flow cytometry, was performed independently in three laboratories. Study 3 examined the histamine release (one laboratory) and the activity of H<sub>2</sub> receptor antagonists and structural analogues (two laboratories). The results showed that high dilutions of histamine ( $10^{-30}$ - $10^{-38}$  M) influence the activation of human basophils measured by alcian blue staining. The degree of inhibition depends on the initial level of anti-IgE induced stimulation, with the greatest inhibitory effects seen at lower levels of stimulation. This multicentre study was confirmed in the three laboratories by using flow cytometry and in one laboratory by histamine release. Inhibition of CD63 expression by histamine high dilutions was reversed by cimetidine (effect observed in two laboratories) and not by ranitidine (one laboratory). Histidine (the inactive analogue) tested in parallel with histamine showed no activity on this model. The authors concluded that in the three different types of experiments, high dilutions of histamine may indeed exert an effect on basophil activity. This activity observed by staining basophils with alcian blue was confirmed by flow cytometry. Inhibition by histamine was reversed by anti-H<sub>2</sub> and was not observed with histidine these results being in favor of the specificity of this effect.<sup>xxii</sup>

In 2009, Chirumbolo *et al* confirmed this inhibition of basophil activation by histamine even at extremely low doses (high dilutions). Their purpose was to dispel concerns about the reproducibility by using rigorously controlled studies. Serial 1:100 (v:v) histamine dilutions (centesimal dilutions, C) and water controls were tested on human basophil responsiveness to anti-IgE antibodies, using flow cytometry. Each dilution step was followed by vertical mechanical shaking (also designed as succussion) at 20 strokes/s. Basophil-enriched buffy coats from healthy blood donors were incubated with  $10^{-4}$  mol/l histamine (2C) and with serially diluted preparations from  $10^{-20}$  mol/l (10C) to  $10^{-32}$  mol/l (16C), then incubated for 30 min with 1 µg/ml goat monoclonal anti-human IgE and basophils stained for immunophenotyping. Results showed that membrane up-regulation of CD203c, which in these experimental conditions proved to be a more consistent activation marker than CD63, was significantly inhibited in samples treated with histamine at the dilutions of 2C (P = 0.001), 12C (P = 0.047), 14C (P = 0.003), 15C (P = 0.036) and 16C (P = 0.009). Control water dilutions/succussions did not show any significant effect.<sup>xxiii</sup>

Ennis reviewed basophil studies to date and delineated a number of inconsistencies from experiment to experiment. She recommends standardization of protocols, triple-blinding, and randomization. She suggests that a single donor should be considered for each experiment, and that negative controls be validated for each experiment. Methods of preparation of all reagents should be standardized. The best methods to detect basophil activation should be determined.<sup>xxiv</sup>

Endler *et al* performed a bibliometric study to provide an overview of fundamental biochemical and biological studies that used high homeopathic potencies, and that were subjected to laboratory-internal, multicenter, or independent repetition trials. They found 24 experimental models in basic research on high homeopathic potencies which were repeatedly investigated. Of these, twenty-two repetitions showed comparable results, 6

repetitions showed different results, and 15 showed no results. Seven models were independently reproduced with either comparable or different results. They comment that:

This relation is fairly well reflected by multicenter studies, i.e. studies that were centrally organized, but carried out by various researchers in different laboratories, namely 66% comparable, 17% different and 17% no effects. Thus multicenter studies seem to be an adequate tool to investigate basic high potency models.<sup>xxv</sup>

The reader is referred to the above study, available on-line in pdf for free, for details on the constituent studies. Of interest, though, is one of the most highly-studied systems: amphibian metamorphosis. The original studies were done by Endler *et al* as early as 1991, and studied the metamorphosis of tadpoles. Thyroxine at ponderal doses accelerates the metamorphosis of tadpoles. In dozens of blinded studies, thyroxine 30x (compared to water) significantly inhibited the metamorphosis of tadpoles, as well as the spontaneous tendency of young frogs to leave the water. Significant effects appeared in as little as a few minutes after exposure of the animals to the thyroxine dilution.

<sup>xxvi,xxvii,xxviii</sup> According to the bibliometric study compiled by Endler *et al*, seven out of a total of eight repetitions of these studies resulted in positive confirmations of the original studies. A total of 10 out of 11 experiments in this field yielded congruent results.

The authors point out that when all of the studies (frogs, basophils, etc.) are compared in detail, methods always differed to a smaller or larger extent in the independent studies. For example, Guedes *et al* used potencies prepared from thyroid glands instead of pure thyroxin as in the Endler experiments.<sup>xxix</sup> In at least three model systems, Endler *et al* identified one relevant parameter crucial for successful repetition of the experiments. In the amphibian metamorphosis model developed by Endler *et al*, only animals from highland frog biotopes consistently respond to a treatment with homeopathically potentized thyroxin, presumably due to a higher endogenous level of thyroxin or higher susceptibility to thyroxin.<sup>xxx</sup>

## **MECHANISM OF ACTION: HOMEOPATHY AND HORMESIS**

In the latter part of the 20<sup>th</sup> Century, conventional medicine has emphasized understanding the mechanism of action of medicines before clinically utilizing a therapy. Complementary/Alternative therapies often suffer from a lack of this understanding, a deficit that has been cited as a reason for avoiding such therapies. Homeopathy, as an alternative therapy, is no exception here.

In the *Organon of the Medical Art*, Hahnemann laid out all the rules necessary for successful prescribing in homeopathic practice. The symptoms of the sick patient gave all the clues needed to prescribe, and all that was needed to understand in the drug was discovered in the provings. Hahnemann said:

This natural law of cure has authenticated itself to the world in all pure experiments and all genuine experiences; therefore it exists as fact. Scientific explanations for how it takes place do not matter very much and I do not attach much importance to attempts made to explain it.<sup>xxxii</sup>

Fortunately for homeopathy in the 21<sup>st</sup> Century, scientists and homeopaths are recognizing the importance of delineating the mechanisms of action of remedies on cells and whole organisms. This may prove to be irrelevant in a clinical setting, or it may yield practical prescribing hints that improve the accuracy of remedy and potency selection.

Regarding the method of action of remedies, Hahnemann said:

Each...medicine, alters the life force more or less and arouses a certain alteration of a person's condition for a longer or shorter time. This is termed the *initial action*. While the initial action is a product of both the medicinal energy and the life force, it belongs more to the impinging potency [of the medicine]. Our life force strives to oppose this impinging action with its own energy. This back-action belongs to our sustentive power of life and is an automatic function of it, called the *after-action* or *counter-action*.<sup>xxxii</sup>

These brilliant observations by Hahnemann almost two centuries ago are being verified by scientific studies today.

The field of hormesis may provide a context in which to evaluate the responses of living systems to homeopathic remedies. Toxicologists employ the concept of hormesis to understand the effects of substances on a multitude of living systems. In brief, hormesis is a dose-responsive phenomenon in which a low dose of a substance stimulates and a high dose inhibits. Specifically, it is a dose-time-response relationship in which an initial dose dependent toxicity response occurs, followed by a compensatory or rebound response, such that at low doses the response becomes greater than the original background state or control group value. High dose treatment groups that experience much greater damage often do not fully compensate or repair all damage up to the conclusion of the experiment. The low dose stimulation appears to be a result of damage-related, compensatory responses.<sup>xxxiii</sup> So we see that in both cases, (homeopathy and hormesis), the reaction of the organism is critical.

Hormesis has been overwhelmingly studied in experimental settings that do not relate clinically at this time. Hormesis studies *pre-conditioning* of living systems. In other words, it is known that injury can be reduced and tissue repair accelerated if a low dose of a toxic agent is given *before* exposure to injury-inducing toxic chemicals or radiation. Homeopathy, on the other hand, is related to hormesis by virtue of being a *post-conditioning* stimulus to living systems. Homeopathic remedies enhance the restorative process, or the compensatory response to damage.<sup>xxxiv</sup>

Using hormesis as a model, the principles of homeopathy can be studied and developed. The concept of similitude (“like cures like”), for example, has been studied extensively by Wiegant and Van Wijk using heat shock proteins (HSP) as markers for cellular recovery. In brief, when cells are damaged by heat stress or toxins, they react with an up-regulation of HSPs, which act as molecular chaperones, facilitating the folding of other cellular proteins. In repair situations, they repair structural damages by forcefully disentangling aggregated proteins, unfolding and refolding them into “re-educated and born again” functional proteins, or targeting improperly folded proteins to specific pathways for degradation. Their role in enhancing stress tolerance and in increasing the survival capacity of cells is well-established.<sup>xxxv</sup>

Different families of HSP are differentially synthesized in response to various stress conditions. In fact, these “molecular symptoms” are characteristic to the specific stressor.

The authors state that these molecular symptoms could be considered “remedy pictures” at the cellular level.

Working with the idea of specific HSPs being produced when healthy cells were treated with specific stressors (as in provings), they sought to determine if applying these stressors in a homologous (isopathic) or heterologous (homeopathic) post-conditioning manner would result in an increase in these same HSPs. The latter would prove the similia principle on a cellular level. They used diluted and vortexed substances (such as arsenite, cadmium, mercury, menadione, and diethyldithiocarbamate) which had been tested on healthy cells in order to derive the resulting pattern of HSP. [Note that the concentrations of the “toxic” substances did not exceed the reciprocal of Avogadro’s number.] The results showed a highly significant correlation between the degree of similarity and survival stimulation factor. The authors call this “unequivocal experimental support...on the similia principle at the cellular level.”

Similar results were obtained using the homologous substances. Interestingly, using the concept of post-conditioning, they found that when using low doses of homologous substances, the capacity to induce HSPs was present only during the early period of recovery. However, during this period of tolerance, increased survival capacity could be induced by application of low doses of heterologous substances. These findings may underlie the observations of the use of the isopathy when applied with correct timing to prevent epidemics (to be discussed later) versus the use of homeopathy to reverse damage that has already set in.

## **MECHANISM OF ACTION: ELECTROMAGNETIC SIGNALS**

Benveniste had performed numerous experiments, with results confirming his electromagnetic (EM) signals theory. In short, his hypothesis states that substances do not actually affect target cells by a key-keyhole mechanism, but rather by emitting EM signals that cause the specific target receptor to resonate. His work was based on these concepts:

1. Every atom and molecule and intermolecular bond emits frequencies.
2. These frequencies can be recorded and replayed to receptors and the specific receptor will vibrate (resonate) at the same frequency.
3. Water is the vehicle for information. The body has 10,000 water molecules for every molecule of protein. A molecule will not transmit its signal in a medium devoid of water. Adding water is not enough- it must be “informed.” (succussion) The water then relays and possibly amplifies the signal.<sup>xxxvi</sup>

The activity of acetylcholine (ACh) was digitized, recorded, and replayed to water. This water was then exposed to isolated guinea pig hearts, causing a statistically significant increase in coronary flow compared to water alone, or digitized water. The effect was similar to that of actual ACh on the hearts. Atropine inhibited the effects of both digitized ACh and ACh. The results indicate that the molecular signal is composed of waveforms in the 0-22KHz range.

Similar studies using ovalbumin digital recordings were performed. In these studies, the recordings were sent as e-mail attachments from France to Chicago. The recordings were played to water, then the water perfused to isolated hearts from ovalbumin

immunized guinea pigs. Both the digitized ovalbumin and physical albumin had statistically positive effects on coronary flow, compared to water and digitized water.

Another study using ACh compared diluted ACh “mixed” in water to diluted ACh vortexed (to achieve violent agitation) in water. The vortexed dilutions, or digitally recorded vortexed dilutions, affected coronary flow to isolated guinea pig hearts with statistically significant results.

Bacteria emit EM signals. Benveniste recorded signals from E coli K1, Staphylococcus, and saline, and performed experiments proving the specificity of these signals. The above studies by Benveniste have been published in peer-reviewed journals.

The now-defunct website [www.digibio.com](http://www.digibio.com) had shown a video an automated plasma coagulation experiment by Benveniste. A computer delivered the EM signal of heparin to water. Plasma was then mixed with water, and the clotting time of the plasma was prolonged, in the same manner as plasma exposed to actual heparin was prolonged. Benveniste also performed similar studies using digital recordings from water treated with heparin 30c.

Recently, a company called Nativis in California announced that they plan to imprint the pattern of medicines on to water or a similar liquid, allowing that liquid to carry the effect of the chemical to the body. They base their hopes on quantum electrodynamics, stating that chemistry is based on the interactions of small packets of electromagnetic radiation or photons. They plan for their drugs to be able to go much further into places like the brain and be able to fight cancer, regulate genetic activity, all while producing less harmful side effects. ([www.nativis.com](http://www.nativis.com))

## THE PROVINGS

In the *Organon*, Hahnemann lays down instructions for conducting pathogenetic trials, or provings, of medicines. Included in his instructions are a number of important observations.

As mentioned previously, the testing of remedies should be performed on healthy individuals of both sexes and all constitutions. Bell *et al* performed a survey of 4400 young adult college students and determined that only 15% could be considered “healthy.”<sup>xxxvii</sup> Accurate assessments of pre-existing symptoms must therefore be made before a proving starts so that these symptoms are not included among the proving symptoms.

The remedies are given to people in a 30c potency (as recommended in the 6<sup>th</sup> edition of the *Organon*) once, allowing the prover to record the initial and then counter-action of the remedy in sequence. The symptoms are recorded, with special note given to the modalities affecting each symptom.

Hahnemann observed that provers differed in their sensitivity to the remedies being tested, with some provers standing out as “sensitive provers,” in that one dose of the remedy would elicit a host of symptoms for that remedy. A person might have this response to one remedy being tested but not to another. The person finding him/herself in the situation of being a sensitive prover for a particular proving would be very valuable, as the primary and secondary (initial and counter-actions) would occur in perfect order. However, most provers do not show such a response, and sometimes require repeated

daily doses of remedies to elicit symptoms. In these cases, the provers should show the various “disease states which this medicine can in general bring to pass, but not their sequence.” Each subsequent dose may take away one or another symptom aroused by the previous dose or it may cause an opposite state. This may cause some confusion as to whether these symptoms are the counter-actions of the prover or reciprocal actions of the medicine. Hahnemann cautions that in these cases, the symptoms should be considered ambiguous until further provings confirm them.

A proving of a remedy is not considered complete until symptoms documented by a prover are all repeats of previously-documented provings.

With the above information in mind, we can better evaluate recent RCTs on provings. The best trials would:

1. Engage a large number of human test subjects so that both sexes, all constitutions, and at least some sensitive provers would be represented.
2. Allow the human test subjects to record their symptoms over at least a couple weeks to increase the chances that the symptoms of the remedy will occur.
3. Be double-blinded, placebo-controlled, and randomized.
4. Utilize a pre-testing period during which the provers could record their baseline symptoms.

Walach *et al* conducted a pilot study employing the above criteria with the exception of having a total of only 11 provers and using only a one-week period to record baseline symptoms. The remedy being tested (cantharis) was an established homeopathic remedy, randomly and blindly selected from a list of 12 established remedies. While their results would have been much more meaningful with a large study population, they were able to find significant increases in symptoms between the baseline and proving symptoms in both the verum and placebo groups, with more symptoms occurring in the verum group, and more of these symptoms being typical for the remedy tested.<sup>xxxviii</sup>

Dominici *et al* improved upon the above study in their own study utilizing two provings of new substances, Etna lava and Hydrogenium peroxidatum. Baseline values were obtained over a 2-week period, and once the study commenced, symptoms were recorded during a one-month period. In addition, symptoms were grouped in categories: existing symptoms showing an increase in intensity and duration (common symptoms), previous symptoms that had not occurred for at least one year (old symptoms), current symptoms that disappeared during the proving (cured), new symptoms that were unfamiliar to the prover, and exceptional symptoms that were new or unusual with respect to intensity and/or duration.

The verum groups produced more symptoms over all than the placebo groups, with the Etna lava group showing high statistical significance. The types of symptoms produced in verum versus placebo were also different, with the new symptoms (46% of the symptoms produced for Etna lava, 44% for Hydrogenium peroxidatum) and exceptional symptoms (13% and 15.5%, respectively) accounting for 59% of the symptoms produced in the verum groups versus 35% in the placebo group (with only 1% in the category of exceptional symptoms). Other differences in symptom classes (mental versus physical, for example) were observed. Of note was the time course of the symptoms. Verum groups experienced appearance of symptoms in the first few days of the provings, with more than 50% of the new symptomatology persisting for at least six

days. In the placebo group, symptoms were registered constantly during the proving, and these symptoms tended to be of much shorter duration (2 days).<sup>xxxix</sup>

## **EVIDENCE IN FAVOR OF HOMEOPATHY: PREVENTION OF EPIDEMICS**

In December 2008, Nosodes 2008: International Meeting on Homeoprophylaxis, Homeopathic Immunization and Nosodes Against Epidemics, was held in Havana, Cuba. Many papers were presented, including studies on food animals, but the most notable one was on the prevention of leptospirosis outbreaks in Cuba. A scientific paper was later published.<sup>xi</sup>

Nosodes are remedies made from diseased substances. For example, psorinum is made from the human scabies pustule, and lyssin is made from the saliva of a rabid dog. Most nosodes used in homeopathic prescribing are proven remedies, enabling their full range of symptoms to be employed.

Nosodes may be applied isopathically as well. As discussed in the hormesis section above, when a low dose of a stressor is applied to a system and then the system is exposed to the stressor in a higher dose, we would expect the pre-conditioning at the low dose to result in stimulation of the organism. The massive pre-exposure prophylaxis with Leptospirosis nosode in Cuba had just this effect.

The leptospirosis study came out of the Finlay Institute, part of the Ministry of Public Health in Cuba. This institute distributes its own Leptospirosis vaccination. Typically, August is the height of the hurricane season in Cuba, and many people are left homeless, flooded, and stressed. Cases of lepto rise dramatically during this time, with thousands becoming infected and many dying. The Finlay Institute's vaccine takes the better part of a year to produce, and 2 million doses will only cover 773,000 people at risk.

In October and November 2007, three provinces of the eastern region of Cuba were affected by strong rainfalls that caused flooding and damage to sanitary, power, and health systems. Two million people were exposed to potentially contaminated water. Finlay Institute prepared a *Leptospira* nosode (nosoLEP) in 200c potency using four circulating strains<sup>3</sup>. The nosode was administered to 92% of the people living in the affected regions, in cooperation with the public health system infrastructure, by week 50. Two doses were given 7-9 days apart to 2,112,257 people by week 50. This was repeated 10-12 months later with 2 oral doses, 7-9 days apart, using the 10m nosode.

The epidemiologic surveillance after the intervention showed a dramatic decrease of morbidity (10 cases) two weeks after and a reduction to zero mortality of hospitalized patients. The number of cases fell from 38 in week 46 to 3-4 cases/week during weeks 49-52 of 2007, significantly lower than the historic median. The reduction was coincident with the coverage of 70% of the population with nosoLEP 200c. This represented a reduction from the predicted trend of 111-461 cases to an actual 38 cases, a 65.8-91.8% reduction. The rest of the country showed no decrease from historic trends in the

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<sup>3</sup> A Bach flower combination similar to Rescue Remedy was also administered.



incidence of leptospirosis, with the number of confirmed cases remaining at 16 per week at the end of 2007.

In weeks 1-41 of 2008, both the intervention region and the rest of the country reported a similar number of cases to the historic median. But by the end of 2008, major differences were found. Weeks 49-52, the number of cases in the intervention region remained significantly lower than the historic median- the modification on trends observed in 2007 persisted a year after the nosode intervention. There were no confirmed cases of leptospirosis in the intervention region in 24 out of 52 weeks, and 40 out of 52 weeks saw 0-2 cases/week. In contrast, the rest of the country had a high number of infected people in the last weeks of the year, and no change in trend for either 2007 or 2008.

It took one week to manufacture 5 million doses of the leptospirosis nosode. Cost of previous yearly vaccination programs: US\$3,000,000. Cost of nosode program: US\$200,000.

## **THE CASE REPORT AND THE RCT**

The homeopathic literature is comprised overwhelmingly of case reports. There are two potential reasons for this. First, in Hahnemann's mind, "like cures like" was a proven theory, confirmed by his meticulous observation and documentation and verified by the cures in the clinical practices of his colleagues and students. This verification was itself documented by thousands of case reports generated by homeopaths in the past 200 years. Most of these cases focused on the nuts and bolts of homeopathy: delineating characteristic symptoms and matching the totality of the symptoms to the simillimum, the curative remedy. By recording these cured cases, other homeopaths were able to appreciate the scope of cure using remedies. Second, it was not until the 1970's that the randomized clinical trial rose to prominence as the acid test for verifying any medical assertions.

As medical diagnostics became more sophisticated, so too did the level of proof required in case reports. Diagnostic names became more specific, and often descriptive of pathological findings, causing the previous diagnostic labels to be viewed skeptically. One might be tempted to therefore discard the lessons learned from all case reports which preceded modern technology, although this would be ill-advised. Homeopathy was and still is based on *observation* of symptoms (signs in our patients). In reality, diagnostic labels are irrelevant. If one carefully studies case reports, it becomes clear that diagnostic labels are helpful in categorizing for epidemiologic purposes, but not so much for homeopathic cures.

Interestingly, a shift is occurring in which a more critical view is being taken of the randomized clinical trial (RCT). Ideally, the RCT has the advantage of objectivity. Very controlled experimental situations can be set up to measure one intervention. The reality of the RCT is emerging as very different.

First of all, in real-life situations, a patient rarely has only one clinical variable amiss. Hahnemann himself recognized that even a localized lesion, like a wound, affects the whole patient, who will in turn manifest other physical and even emotional symptoms. It

is the unique way in which the whole patient is affected that enables the homeopath to individualize the remedy selection for the patient. In essence, from the perspective of the RCT, all patients are considered clinically equal based on a diagnostic name, while in reality they each are highly differentiated and complex. It is these unrecognized differences that account for the less than 100% effectiveness of most conventional therapies.

Along these lines of the RCT only addressing one variable, homeopaths and patients know that disappearance of a symptom does not equate to improved quality of life (QoL). In homeopathy, when an improved QoL does not occur concurrent with the disappearance of a symptom, this situation is categorized as either palliation or suppression and presages the appearance of more serious symptoms. This calls into question the duration of the follow-up period of any given intervention, as well as the scope of “effects” intentionally observed by the researchers. For example, homeopaths recognize that the inappropriate disappearance of one symptom affecting one organ system may manifest as the appearance of another ailment in a totally different organ system. Conventionally-speaking, the patient may seek help from a different “ologist.” Accordingly, when measuring the effect on the disappearance of, say skin eruptions from a specific drug intervention, according to homeopathic principles, the researcher would need to conduct a long-term follow-up, perhaps over years, and document any problems that arose in different organ systems while including emotional/behavioral symptoms as significant. Obviously, this would not be a favorable scenario for quick and efficient drug approval.

Thirdly, the RCT is not possible with many conditions in which assigning a patient to the placebo group would be unethical or inhumane. This applies to serious medical conditions as well as surgical conditions.

Fourth, some diseases are uncommon, and gathering enough cases for a statistically meaningful RCT may not be possible.

Fifth, the RCT is subject to manipulation, not just in the methods of statistical analysis utilized, but also in the very decision to publish the study or not. Dr. John P. A. Ioannidis, a meta-researcher and one of the world’s foremost authorities on the credibility of medical research, has published many peer-reviewed papers on why most published findings are false, and why publication practices may distort science.<sup>xli,xliii</sup> In addition to the recognized variables such as sample size, (large studies are more likely to yield true results), Dr. Ioannidis also statistically demonstrates why other factors can skew results. He includes in his analysis the “effect” size (larger effects, like smoking on cancer, are likely to be true, whereas smaller effects like genetic risk factors for multigenetic diseases are less likely to be true); the number of tested relationships in a scientific field (hypothesis-generating experiments are less likely to be true than phase III RCTs or meta-analysis thereof); flexibility in designs, definitions, outcomes, and analytical modes (flexibility increases the potential for transforming what would be negative into positive results, i.e. bias); financial and other interests and prejudices (conflicts of interest and prejudice may increase bias and are typically inadequately and sparsely reported); the “heat” in a scientific field (the hotter a scientific field, with more teams involved, the less likely the research findings are to be true due to the drive to pursue and disseminate the most impressive positive results- or negative results if another team has found a positive association on the same question).

Of direct relevance to research in homeopathy are Dr. Ioannidis' findings that prestigious investigators may suppress via the peer review process the appearance and dissemination of findings that refute their findings. This prejudice may not necessarily have financial roots, but may reflect the unwillingness to give up a lifetime of research devoted to a specific paradigm.

In a paper published in JAMA in 2005, Dr. Ioannidis shows that of the 49 most-cited papers on the effectiveness of medical interventions, published in highly visible journals from 1990-2004, one-quarter of the RCTs and 5 of 6 non-randomized studies had already been contradicted or found to have been exaggerated by 2005.<sup>xliii</sup> Along these lines, the literature suffers from a paucity of negative data; or, in trials in which the results were indeed negative, they were published such that the results would appear positive.<sup>43</sup>

For many reasons, successful publication may be more difficult than in the past. In the biological sciences, data acquisition has increased dramatically while space for publication of findings has not. Demand for publication space is further constricted by the disproportionate prominence of a few journals. And the demand on these journals is to attract specific papers, such as influential trials that generate publicity and profitable reprint sales. This results in what Dr. Ioannidis terms the "gaming" of impact factors<sup>4</sup>. Due to the relative obscurity of many journals, publication "often signifies 'final registration into oblivion'" according to Dr. Ioannidis. One unfavorable consequence is the reduction in diversity of areas under exploration.<sup>43</sup>

We are all familiar with the many human drugs that have been removed from the market in the past few years due to adverse events, only to reveal undisclosed studies from the pharmaceutical manufacturers. This publication bias extends to medical conferences as well. Dr. Otis Brawley, writing for CNN.com, says:

[Medical meetings] began as forums for scientists to meet and discuss findings and generate ideas. They offer opportunities for physicians to learn about new studies and possible new treatments...But over the past several decades, these gatherings have more and more become venues for drug companies and medical device manufacturers to tell physicians about their drugs and medical hardware. Today, much of the presented research is sponsored by industry, and these medical meetings are increasingly an opportunity for companies to make a name for themselves by promoting their products.<sup>xliv</sup>

In the same vane, even a well-done RCT with a highly-representative patient sampling (in quality and quantity) may focus on one finding that leads to an assumption of this being the best treatment course of a patient based on the lack of RCTs for other treatment options. For example, a pet food manufacturer may perform a RCT on their prescription diet, showing that it extends time from diagnosis until death versus a usual commercially-available supermarket diet. Since this may be the only RCT on this condition, the assumption might be to feed only this prescription diet, as the

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<sup>4</sup> The impact factor for a journal is the average number of citations received per paper published in that journal during the preceding two years. It is calculated as  $A/B$ , where  $A$ = the number of times articles published in the preceding two years were cited in indexed journals and  $B$ = the total number of citable items published in that journal in the preceding two years. Citable items typically are articles, reviews, proceedings, or notes, but not editorials or letters to the editor.

preponderance of evidence is now in its favor. However, based on clinical experience, practitioners may have discovered other feeding protocols that work just as well if not better. It may be years until a pet food manufacturer explores this other avenue and publishes the results- if it will be profitable for them.

From a different perspective, the case report may indeed be the gold-standard. According to Dr. Jan Vandenbroucke, medical science has two views, one which emphasizes discovery and explanation, and the other which emphasizes evaluation of interventions. This leads to opposite research hierarchies, with randomization at the top for evaluation and at the bottom for discovery and explanation. Likewise, the case report sits at the top of the hierarchy of study designs for discovery and explanation:

1. Anecdotal: case reports and series, findings in data, literature
2. Case-control studies
3. Retrospective follow-up studies
4. Prospective follow-up studies
5. Randomized controlled trials

In short, the case report can serve to report the discovery of a new medical intervention, with the intent that it will be followed by further investigation into its efficacy. Once that intervention has a high probability of efficacy, as determined by 2-4 above, a RCT can be executed to evaluate the intervention at the highest level. In fact, Vandenbroucke suggests that the hierarchy which seeds the RCT at the top might be called a “hierarchy of prior odds.”<sup>xlv</sup>

Case-based reasoning (CBR) is solving a new problem by remembering a previous similar situation and reusing information and knowledge of that situation.<sup>xlvi</sup> Re-using past cases is a powerful and frequently applied way to solve problems for humans. Cognitive psychological research also supports this claim. In reality, veterinarians do this all the time, probably more frequently than they consult PubMed for literature searches on the best way to treat a case that they are presented with. Case reports and case series often reflect real-life situations for veterinarians while eliminating the statistical analysis that characterizes RCTs and which may discourage clinically-oriented veterinarians from reading further. Even using Veterinary Information Network (VIN), a mainstay at our practice, is often based on gleaning the CBR from the VIN consultants. Even though the original idea for a treatment may have originated from a RCT, it is the CBR that establishes whether or not we will adapt that treatment to our arsenal.

To date, almost all homeopathy case reports can be found exclusively in the homeopathic publications. Software programs, used to assist homeopaths in finding the simillima, contain extensive libraries with searchable case reports based on symptoms and sometimes diagnostic names. The Academy of Veterinary Homeopathy (AVH) publishes a quarterly journal that often features case reports. This author has published many case reports in this periodical. Likewise, the British Association of Homeopathic Veterinary Surgeons (BAHVS) also publishes its own periodical containing case reports.

As of the submission of this manuscript, (December 16, 2010), the author has had a case report accepted for publication in the Journal of the American Animal Hospital Association. The case is a cure of a dog with nasal aspergillosis using the homeopathic remedy aurum metallicum. This was a case report of high quality, in that the recognized accepted diagnostic standards were performed before and after homeopathic treatment, and the dog was given the conventional treatment known to be most successful at that

time, (and to date still compares favorably to all other available treatments). The dog had been refractory to the conventional treatment, but after homeopathic intervention at a 30c potency, the dog showed a rapid improvement over two weeks and made a full recovery. Post-treatment testing showed removal of all aspergillus organisms. This was the second such case report published by this author on this condition using the same remedy; however, the first case report did not include follow-up studies, even though that dog made a full clinical recovery and has not relapsed in the subsequent six years since treatment.

The case report above centered its success on the disappearance of the fungal organisms. Interestingly, homeopathic prescribing is not dependent on etiologic agents for successful prescribing, and the successful prescription was actually based on the clinical presentation with the added information of bone destruction provided by the CT scan. The paper, as it will be published, does not focus on the homeopathic methodology involved in selecting the curative remedy. This is a major difference from case reports as they appear in the homeopathic literature.

Finally, homeopathy case reports can produce the “wow” factor. In other words, when enough cases for a clinical trial or even a case series are not available, cures of otherwise incurable cases, like advanced nasal aspergillosis or certain cancers, can serve to make the veterinary medical community take a second look at this modality.

## **CLINICAL TRIALS**

RCTs can serve many purposes for homeopathy. Among the more important uses is the demonstration of activity in ultramolecular dilutions, and the testing of the effectiveness of homeopathy for specific clinical conditions. Moreover, with each RCT that shows effectiveness of homeopathy for a specific condition, skepticism about the validity of homeopathy in general is mitigated.

Of note are the dozens of non-RCT published in the peer-reviewed literature. These include observational studies, cohort studies, outcome studies, cost-effectiveness studies, patient satisfaction surveys, etc. With respect to the RCT, the human side of homeopathy is far ahead of the veterinary side. Over 127 placebo-controlled trials in human medicine have been published.

Focusing on the human studies, we can learn more than just the results of the targeted outcomes (homeopathy worked v. did not work) from these clinical trials.

A well-designed clinical trial in homeopathy should include the following:

1. Individualized remedy prescriptions
2. Skilled homeopaths, or a team of skilled homeopaths to increase the chance that the correct remedy was selected
3. Adequate time post-remedy administration to observe for benefits from the remedy
4. Evaluation of all the benefits to the patient, and not just the “targeted” outcome of the trial.

On the surface, a clinical trial to see if homeopathy “works” for a given condition should yield a straight up or down answer. In reality, any given clinical trial in homeopathy is fraught with complexity issues. When an incorrect remedy is prescribed,

the lack of response relegates that patient to the “failed” group. However, when an incorrect remedy is prescribed, this patient is actually joining the placebo group, as an incorrect remedy should have no more benefit than a placebo. In other words, in the designated “verum” group, there are patients receiving active or inactive remedies. It would be beneficial to know in advance if the correct remedy was selected.

The skill of the homeopath involved is critical in this regard. No homeopath boasts 100% success rates in clinical practice. Given the choice of over 2000 remedies for any given patient, an added dimension of complexity is introduced. The individual success rate of the practitioner involved in the study should be factored in to the analysis of results. To my knowledge, this has not been considered to date. The issue is addressed, instead, by using a team of skilled homeopaths to increase the chances that successful prescriptions have been made. Mathie *et al* have also conducted studies in England with homeopaths that treat humans as well as those that treat animals, and they have delineated which conditions are treated with the highest success rates by homeopathic practitioners.<sup>xlvii,xlviii</sup> For animals, they have used this information to design studies in canine atopy, under the assumption that the chances of selecting the true simillimum will be increased for each patient. However, the second phase of this study, a non-randomized clinical trial in which remedies were prescribed for patients with intractable atopy, did not measure the individual success rates of these specific prescribing practitioners.<sup>xlix</sup>

To circumvent the problem of incorrect remedies being prescribed in a clinical trial, a pre-screening trial can be conducted. Frei *et al* conducted such a trial for ADHD. Prior to enrolling children in a double-blind placebo-controlled ADHD study, a pre-screening trial was conducted in which it took a median of five months (range 1-18) and three different single remedies (range 1-9) (given sequentially) to determine the active verum for the study participants. The results of Frei’s subsequent RCT were positive.<sup>1</sup> This contrasted with an ADHD study by Jacobs *et al* in which the results were negative, but in which no pre-screening for the correct remedy was performed.<sup>li</sup>

In a study in the publication process, presented at the Academy of Veterinary Homeopathy Annual Conference and Meeting in November 2008, Ellinger described the successful homeopathic treatment of diarrhea in calves. Similar to the study by Frei *et al*, the researchers first delineated the most likely remedies for calf diarrhea on each particular farm. This was accomplished in a step-wise manner. Starting in 2000, Ellinger conducted a series of homeopathy courses relevant to diseases in cattle. 320 farmers participated. Because the exchange of experience (homeopath to farmer and farmer to homeopath) played a central role in the course, Ellinger was able to delineate which diseases could be treated in a relatively simple and successful way, and which farmers were grasping the methods of homeopathic prescribing well.

Unlike humans or companion animals who come to the practitioner from a variety of genetic backgrounds and environments, cattle live in large groups under the same circumstances of climate, housing, nutrition, care, etc. and have a similar genetic background. When these animals show symptoms of the same disease at the same time, and they exhibit more or less the same symptoms, a *genus epidemicus*<sup>5</sup> can very often be administered.

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<sup>5</sup> The remedy that is determined from combining all the symptoms of all the patients suffering from the same epidemic.

Working with the farmers who appeared to be good observers of symptoms needed for successful homeopathic prescribing, remedies for calf diarrhea specific to each farm were determined. Double-blind placebo-controlled clinical trials were then conducted showing a statistically significant effect of the homeopathic remedies over placebo.<sup>lii</sup>

When a pre-screening trial is not feasible, physiologic markers that could predict the accuracy of the remedy selection would be useful. Bell's group at the University of Arizona are looking at a number of markers in humans. EEGs are delineating differences in responders versus non-responders.

Time-dependent sensitization (TDS) is a proposed mechanism for action of homeopathic remedies in fibromyalgia (FM) patients. In a 4-month randomized, placebo-controlled double-blind trial, individualized homeopathic remedies were given to FM patients, and alpha-1 and alpha-2 EEG waves (a measurement of TDS) were measured during olfactory administration of the verum or control solutions. At four months, the patients were given the opportunity to switch from one trial group to the other in an additional two months crossover phase. At three months, the EEG measurements of the active group increased significantly, while those of the placebo group decreased. At six months, those that stayed on active continued to increase, while those that switched from verum to placebo having not done as well clinically had a decrease in their response to the level of the placebo group's response. Consistent with the TDS hypothesis, sniff alpha-1 and alpha-2 increases at six months versus baseline correlated with total amount of time on active remedy over all subjects, not with dose changes or clinical outcomes in the active group.<sup>liii</sup> Those who did best on the remedies ("exceptional responders") had the strongest alpha response when sniffing the remedy, suggesting these EEG measurements as early biomarkers of individualized homeopathic medicine effects in patients with FM who later exhibit exceptional outcomes.<sup>liv</sup>

Bell *et al* have studied the differences in beta cordance (EEGs) before and after sniffing either pulsatilla or sulphur in either pulsatilla or sulphur remedy-type people, respectively. (Remedy types were determined by a questionnaire.) Distinct differences were found in the EEGs which reflected metabolism in the brain. These findings held true when 6c, 12c, or 30c were sniffed at different visits. These findings suggest the possibility of objective markers to identify remedy types in people.<sup>lv</sup>

Brooks et al (2009) studied changes in the Profile of Mood States (POMS) Tension Scale when patients classified as either "high hostile" or "high addiction sensitivity" were given either nux vomica or coffea cruda. Marked differences in the mean tension changes were observed, indicating that who gets the remedy interacts with the remedy given.<sup>lvi</sup>

Polysomnography is a multi-parametric test used in the study of sleep. It entails a recording of the biophysiological changes that occur during sleep, and measures such bodily functions as EEG, eye movements (EOG), muscle activity or skeletal muscle activation (EMG), and ECG. In a study performed by Bell et al, young male and female subjects ages 18-31 were categorized as either "cynical hostility" or "anxiety sensitivity" (but not both) based on standardized personality scales. At-home polysomnographic recordings were then obtained on successive pairs of nights once per week for a total of eight recordings (nights 1,2,8,9,15,16,22,23). Subjects (N=54) received placebo pellets on night 8 (single-blind) and verum pellets on night 22 (double-blind) in 30c doses of either Nux vomica or Coffea cruda. Subjects completed daily morning sleep diaries and weekly Pittsburgh sleep quality index scales, as well as profile of mood states scales at

bedtime on polysomnography nights. Verum remedies significantly increased PSG total sleep time and NREM, as well as awakenings and stage changes. Changes in actigraphic and self-rated scale effects were not significant. Findings were similar though not identical to those reported in animals with the same remedies. The authors postulated that possible mechanisms included initial disruption of the nonlinear dynamics of sleep patterns by the verum remedies.<sup>lvii</sup>

Finally, in designing clinical trials, global improvements need to be measured rather than just one targeted outcome. Human medicine has many scales for measuring quality of life, and these surveys can be taken before, during, and after homeopathic treatment to further assess global health changes in the patient. In veterinary homeopathy at this time, no standardized global health measurements are being assessed. This may be due to the paucity of studies in small animal homeopathy versus in food animals in which it is indeed more relevant to study one outcome parameter, like duration of diarrhea in neonates. One can see, however, how such QoL measurements might be very relevant in small animal homeopathy in which longevity of patients is desired along with their comfort and perceived happiness.

## **META-ANALYSIS**

The meta-analysis is only as good as the studies that it includes. In general terms, the constituent studies should all be as similar as possible so that the measured outcome accurately reflects the goal of the meta-analysis. Just as in the RCT, the meta-analysis in homeopathy has special considerations. Obviously, poor quality clinical trials will result in skewing the outcome to unfavorable, just as selecting studies of high quality with only favorable results would skew the outcome in the opposite direction.

A high-quality meta-analysis should be composed of studies in which:

1. The trials were randomized, blinded, and peer-reviewed.
2. Remedies were selected based on *individualization* for each patient with no restriction on potency, repetition, or remedy selected.
3. One remedy was given at a time.
4. Homeopathy (versus isopathy) was tested.
5. The constituent studies all commenced at the same time. For example, studies might commence after a phase-in period in which the simillimum is found (as in Frei's ADHD study) or they might commence at the first prescription.

Further, the meta-analysis should meet the following criteria:

6. An exhaustive literature search was performed so that *all* studies meeting the incorporation criteria are included.
7. Constituent studies are all identified (citations provided) and the peer-review process should include evaluating these studies for their suitability.
8. Criteria for matching the conventional to the homeopathic trials should be clearly stated, and this matching should include quality of the trials.
9. Researchers should be subject to full disclosure to avoid agenda-driven bias.

A high-quality meta-analysis was published in *Lancet* by Linde, et al in 1997. It utilized an exhaustive search for studies from computerized bibliographies, contacts with researchers, institutions, manufacturers, individual collectors, homeopathic conference



proceedings, and books. All languages were included. 186 trials were identified, of which 119 met the inclusion criteria, and 89 had adequate data for the meta-analysis. The study concluded that the results were not compatible with the hypothesis that the clinical effects of homeopathy were completely due to placebo. However, they found insufficient evidence that homeopathy was clearly efficacious for any single clinical condition and suggested further rigorous and systematic research.<sup>lviii</sup> Cucherat et al reached similar conclusions in their meta-analysis published in 2000.<sup>lix</sup>

Shang et al published a highly controversial meta-analysis that concluded that the effects of homeopathy were no more than placebo effects.<sup>lx</sup> This meta-analysis has been widely criticized, including by one of its sponsors, the International Review Board of the Complementary Medicine Evaluation Programme (PEK) of the Swiss Federal government. “There is a consensus among the review board members that the final PEK process deviated from what would have been expected by conventional standards.” Fisher, Director of Research at the Royal London Homoeopathic Hospital, has published a critique of the study. He notes that of the 110 trials of homeopathy and 110 conventional trials, the final analysis used only 21 homeopathic studies and 9 conventional ones, and eventually only 8 and 6, respectively, citing their “larger, higher quality.” However, the lack of transparency in the study raised many unanswered questions. First of all, the matching of the conventional to homeopathic studies was not clearly stated. Secondly, the studies were not well-matched, as the homeopathic studies were of higher quality. Shang indeed acknowledges that it is well-established that higher quality studies are less likely to be positive than those of lower quality. Amazingly, no transparency exists for the final 8 studies included in the analysis, including references, information on diagnoses, number of patients, etc. Egger, one of the authors and a publicly critical opponent of homeopathy, refused to disclose the identity of the 8 trials. Fisher states:

But perhaps the most telling single criticism of this meta-analysis is that it fails, on multiple counts, to meet the generally accepted standards for meta-analysis—the QUOROM statement (Quality of Reports of Meta-Analyses of Randomised Controlled Trials), published in *The Lancet* itself in 1999.<sup>lxi</sup>

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<sup>i</sup> Winston, JW *The Faces of Homeopathy: an illustrated history of the first 200 years.* Great Awk Publishing, Taw, New Zealand. 1999. p50.

<sup>ii</sup> *ibid*

<sup>iii</sup> Hahnemann, S. *Materia Medica Pura*, as it appears in ReferenceWorks 2006 software program, Kent Homeopathic Associates, San Rafael, CA.

<sup>iv</sup> Ives JA, Moffett JR, et al. Enzyme stabilization by glass-derived silicates in glass-exposed aqueous solutions. *Homeopathy* 2010;99:15-24

<sup>v</sup> Rey L. Thermoluminescence of ultra-high dilutions of lithium chloride and sodium chloride. *Physica (A)*, 2003;323:67-74.

<sup>vi</sup> van Wijk R, Bosman S, van Wijk EP. Thermoluminescence in ultra-high dilution research. *J Alternative Complementary Med* 2006;12:437-443.

<sup>vii</sup> *ibid*

<sup>viii</sup> Shui-Yin Lo, "Anomalous State of Ice," *Modern Physics Letters B*, 10,19(1996):909-919.

- 
- <sup>ix</sup> S.Y. Lo and B. Bonavida (eds.), Proceedings of the First International Symposium on I<sub>E</sub> Water Clusters. Singapore: World Scientific, 1998.
- <sup>x</sup> Baumgartner S, Wolf M, Skrabal P, et al. High-field 1H T(1) and T(2) NMR relaxation time measurements of H<sub>2</sub>O in homeopathic preparations of quartz, sulfur, and copper sulfate. *Naturwissenschaften* 2009 96(9):1079-89.
- <sup>xi</sup> Demangeat J-L. NMR water proton relaxation in unheated and heated ultrahigh aqueous dilutions of histamine: Evidence for an air-dependent supramolecular organization of water. *Mol. Liquids* 2009 144:32-39.
- <sup>xii</sup> Ibid (Ives)
- <sup>xiii</sup> Chaplin, M. Water Structure and Science, <http://www1.lsbu.ac.uk/water/memory.html>. Last updated May 8, 2010. Visited May 31, 2010.
- <sup>xiv</sup> Elia V, Niccoli M. New Physico-chemical properties of extremely diluted aqueous solutions. *J Therm Anal Calorim* 2004; 75:815-836.
- <sup>xv</sup> Elia V, Elia L, et al. Physico-chemical properties of aqueous extremely diluted solutions in relation to ageing *J Therm Anal Calorim* 2008; 93:1003-1011.
- <sup>xvi</sup> Roy R, Tiller WA, et al. The structure of liquid water; novel insights from material research; potential relevance to homeopathy. *Mater res Innovations* 2005; 9:93-124.
- <sup>xvii</sup> Chikramane PS, Suresh AK et al. Extreme homeopathic dilutions retain starting materials: A nanoparticulate perspective. *Homeopathy* 2010; 99: 231-242.
- <sup>xviii</sup> Maity T, Ghosh D, et al. Effect of dielectric dispersion on potentised homeopathic medicines. *Homeopathy* 2010; 99(99-103).
- <sup>xix</sup> Ibid. Chaplin.
- <sup>xx</sup> Witt, CM, Bluth, M, et al. The *in vitro* evidence for an effect of high homeopathic potencies- A systematic review of the literature. *Complement Ther Med.* 2007; 15(2): 128-38.
- <sup>xxi</sup> Davenas, F, Beauvais, J, et al. Human basophil degranulation triggered by very dilute antiserum against IgE. *Nature.* 1988;333(6176):816-818.
- <sup>xxii</sup> Belon P, Cumps J, et al. Histamine dilutions modulate basophil activation. *Inflamm Res.* 2004; 53(5): 181-188.
- <sup>xxiii</sup> Chirumbolo S, Brizzi M, et al. Inhibition of CD203c membrane up-regulation in human basophils by high dilutions of histamine: a controlled replication study. *Inflamm Res.* 2009; 58(11):755-764.
- <sup>xxiv</sup> Ennis, m. Basophil models of homeopathy: a skeptical view. *Homeopathy.* 2010; 99(51-56).
- <sup>xxv</sup> Endler PC, Thieves K, et al. Repetitions of fundamental research models for homeopathically prepared dilutions beyond 10<sup>-23</sup>: a bibliometric study. *Homeopathy.* 2010; 99:25-36.
- <sup>xxvi</sup> Endler PC, Pongratz W, van Wijk R, Kastberger G, Haidvogel M. Effects of highly diluted succussed thyroxine on metamorphosis of highland frogs. *Berlin J Res Hom* 1991; 1: 151-160.
- <sup>xxvii</sup> Endler PC, Pongratz W, Kastberger G, Wiegant FAC, Haidvogel M. Climbing activity in frogs and the effect of highly diluted succussed thyroxine. *Br Homeopath J* 1991; 80: 194-200.

- 
- <sup>xxviii</sup> Endler PC, Pongratz W, Smith CW, Schulte J. Non-molecular information transfer from thyroxin to frogs with regard to 'homoeopathic' toxicology. *Vet Hum Toxicol* 1995; 37(3): 259–260.
- <sup>xxix</sup> Guedes JRP, Ferreira CM, Guimaraes HMB, Saldiva PHN, Capelozzi VL. Homeopathically prepared dilution of *Rana catesbeiana* thyroid glands modifies its rate of metamorphosis. *Homeopathy* 2004; 93: 132–137.
- <sup>xxx</sup> Welles SU, Suanjak-Traidl E, Weber S, et al. Pretreatment with thyroxine (10e-8) and the effect of homeopathically prepared thyroxin (10e-30) on highland frogs – a multi-researcher study. *Res Compl Med/Forsch Komplementarmed* 2007; 14: 353–357.
- <sup>xxxii</sup> Hahnemann S. *Organon of the Medical Art*. Birdcage Books, Redmond, VA. 1996
- <sup>xxxiii</sup> *ibid.* p107
- <sup>xxxiiii</sup> Calabrese, EJ and Jonas, WB. Homeopathy: Clarifying its relations to hormesis. *BELLE Newsletter* 2010; 16(1):4-10.
- <sup>xxxv</sup> *Ibid.*
- <sup>xxxvi</sup> Wiegant F, Van Wijk R. The similia principle: Results obtained in a cellular model system. *Homeopathy* 2010;99(1):3-14.
- <sup>xxxvii</sup> [www.digibio.com](http://www.digibio.com). Note: Website last visited 2001 and no longer exists.
- <sup>xxxviii</sup> Bell et al. 2007. As presented at Liga 2010, Redondo Beach, CA, May 20,2010.
- <sup>xxxix</sup> Walach H, Sherr J, et al. Homeopathic proving symptoms: result of a local, non-local, or placebo process? A blinded, placebo-controlled pilot study. *Homeopathy*. 2004; 93:179-185.
- <sup>xl</sup> Dominici G, Bellavite P, et al. Double-blind, placebo-controlled homeopathic pathogenetic trials: Symptom collection and analysis. *Homeopathy*. 2006: 95:123-130.
- <sup>xli</sup> Bracho G, Varela E, et al. Large-scale application of highly-diluted bacteria for Leptospirosis epidemic control. *Homeopathy*. 2010;99: 156-166.
- <sup>xlii</sup> Ioannidis, JPA. Why most published research findings are false. *PLoS Med*. August 2005; 2(8);e124
- <sup>xliii</sup> Young, MA, Ioannidis, JPA, et al. Why current publication practices may distort science. *PLoS Med*, Oct. 2008, 5(10):e201
- <sup>xliiii</sup> Ioannidis JPA. Contradicted and initially stronger effects in highly cited clinical research. *J Am Med Assoc*. 2005;294:218–228.
- <sup>xliv</sup> Brawley O. Bad medical writing hurts public health. <http://www.cnn.com/2010/OPINION/06/08/brawley.medical.writers/index.html?hpt=C2>  
Last visited 6/13/10.
- <sup>xlv</sup> Vandenbroucke JP. Observational research, randomized trials, and two views of medical science. *PLoS Med*. 2008 March; 5(3):e67.
- <sup>xlvi</sup> Aamodt A, Plaza E. Case-based reasoning: Foundational issues, methodological variations, and system approaches. 1994. *AI Communications*. IOS Press, 7(1) 39-59.
- <sup>xlvii</sup> Mathie RT, Robinson TW. Outcomes from homeopathic prescribing in medical practice: a prospective, research-targeted, pilot study. *Homeopathy*, 2006: 95:199–205.

---

<sup>xlvi</sup> Mathie RT, Hansen L, Elliott MF, Hoare J. Outcomes from homeopathic prescribing in veterinary practice: a prospective, research-targeted, pilot study. *Homeopathy*. 2007 Jan;96(1):27-34.

<sup>xlix</sup> Hill PB, Hoare J, Lau-Gillard P, Rybnicek J, Mathie RT. Pilot study of the effect of individualised homeopathy on the pruritus associated with atopic dermatitis in dogs. *Veterinary Record* 2009; 164 (issue 12); 365-370.

<sup>l</sup> Frei H, Evert R, et al. Randomised controlled trials of homeopathy in hyperactive children: treatment procedure leads to an unconventional study design. Experience with open-label homeopathic treatment preceding the Swiss ADHD placebo controlled, randomized, double-blind cross-over trial. *Homeopathy*. 2007; 96(1):35-41.

<sup>li</sup> Jacobs J, Williams A-L, Girard C, Njike VY, Katz D. Homeopathy for attention-deficit/hyperactivity disorder: a pilot randomized-controlled trial. *Journal of Alternative and Complementary Medicine*, 2005;11:799–806.

<sup>lii</sup> Ellinger L. Homeopathic research: Diarrhea in calves. Proceedings of the Academy of Veterinary Homeopathy Annual Conference and Meeting, November 2008, Santa Fe, NM.

<sup>liii</sup> Bell IR, Lewis DA 2<sup>nd</sup>, et al. EEG alpha sensitization in individualized homeopathic treatment of fibromyalgia. *Int J Neurosci* 2004; 114(9): 1195-220.

<sup>liv</sup> Bell IR, Lewis DA 2<sup>nd</sup> et al. Electroencephalographic cordance patterns distinguish exceptional clinical responders with fibromyalgia to individualized homeopathic medicines. *J Altern Complement Med* 2004; 10(2):285-99.

<sup>lv</sup> Bell et al, 2010, in progress. Summary presented at Liga 2010 in Redondo Beach, CA, May 19, 2010.

<sup>lvi</sup> Brooks et al 2009 as presented by Bell at Liga 2010 in Redondo Beach, CA, May 19, 2010.

<sup>lvii</sup> Bell IR, Howerter A, et al. Effects of homeopathic medicines on polysomnographic sleep of young adults with histories of coffee-related insomnia. *Sleep Med* 2010; Jul 27 (Epub ahead of print).

<sup>lviii</sup> Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. Klaus Linde; Nicola Clausius; Gilbert Ramirez; Dieter Melchart; et al *The Lancet*; Sep 20, 1997; 350, 9081.

<sup>lix</sup> Cochlear M, Haugh MC, et al. Evidence of clinical efficacy of homeopathy. A meta-analysis of clinical trials. *Eur J Clin Pharmacol*. 2000 Apr;56(1):27-33.

<sup>lxlx</sup> Shang A, Huwiler-Müntener K, et al. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *Lancet*. 2005 Aug 27-Sep 2;366(9487):726-32

---

<sup>lxi</sup> Fisher, P. Homeopathy and the Lancet. eCAM 2006 3(1):145-147;  
doi:10.1093/ecam/nek007