

GUEST EDITORIAL

## All Evidence Is Equal, but Some Evidence Is More Equal than Others: Can Logic Prevail over Emotion in the Homeopathy Debate?

IRIS R. BELL, M.D., M.D.(H.), Ph.D.

In his classic political satire *Animal Farm*,<sup>1</sup> George Orwell described a fantasy world in which having total power gradually corrupts and distorts the initially idealized societal commandments articulated by the farm animals who have successfully risen up against a common enemy (i.e., the farmers, or people). In the end, the commandment that “all animals are equal” drifts into “all animals are equal, but some animals are more equal than others.” Unfortunately, allopathic medicine (i.e., conventional mainstream medicine in its politically dominant position) has reached an analogous juncture in its history of considering evidence. The recent Shang et al. meta-analysis study<sup>2</sup> (see also special section pp. 779–785 in this issue) and the accompanying editorials pronouncing the “end of homeopathy”<sup>3</sup> and the “growth of truth”<sup>4</sup> in the prestigious British journal *The Lancet* expose an Orwellian selectivity and bias in considering facts, as well as an illogic, under the aegis of “evidence-based medicine.” The Shang et al. paper concluded that “the clinical effects of homeopathy are placebo effects” on the basis of 8 unspecified homeopathic studies and 6 unspecified conventional (allopathic) studies out of an original total of 110 studies of each type on the same variety of conventionally diagnosed conditions.

*The Lancet’s* editorial stance raises grave concerns about logic, fairness, and rationality in *The Lancet’s* interpretation and use of the evidence, for several reasons: First, the sub-analysis on which the main conclusions are based did not specify which 8 papers of the original 110 homeopathic or 6 papers of the original 110 allopathic papers were used. This lack of reporting transparency and precision is typically not tolerated for allopathic medical reports. For instance, the Consolidated Standards of Reporting Trials (CONSORT) statement requires a full disclosure of outcomes of all initially en-

rolled patients in a detailed flow chart<sup>5</sup>; but the lack of comparable details was tolerated for the identity of the small number of actual studies used for the Shang et al. meta-analysis conclusions.

Second, the Shang et al. paper is one meta-analysis out of several published meta-analyses (the others have been largely favorable to what they claim is “homeopathy”),<sup>6–8</sup> based on an incomplete and not up-to-date selection of extremely heterogeneous randomized controlled trials (RCTs) encompassing multiple different allopathic diagnoses and using interventions that are only sometimes considered homeopathic by homeopaths. For example, isopathy (using a homeopathically prepared specific agent that triggers specific local symptoms) is not homeopathy by definition,<sup>9</sup> but it has been included in most meta-analyses of homeopathy. A single remedy chosen on the basis of an allopathic diagnosis without regard to its homeopathic indications is not homeopathy<sup>9</sup>; but numerous allopathically “high quality” RCT studies that enter meta-analyses, such as that of Shang et al., ignore this major problem in external ecologic validity. Furthermore a remedy acts homeopathically only when it is homeopathic in its pattern of effects on an individualized basis (i.e., similar but not identical to the pattern of global and local disease in the patient as a whole), an issue for population validity.

An incorrectly chosen remedy for a patient (a not uncommon occurrence in clinical reality) is also not homeopathic and therefore constitutes an inactive “active” intervention that degrades the average outcome of the active/verum group. No RCT studies of homeopathy, and thus no meta-analyses, have as yet accommodated this ecologic validity issue in their designs other than sometimes requiring high homeopath confidence ratings in remedy choice as an inclusion criterion.<sup>10</sup> The problem of incorrect remedy se-

Program in Integrative Medicine, Departments of Family & Community Medicine, Medicine, Psychiatry, and Psychology, The University of Arizona College of Medicine; and the Mel and Enid Zuckerman Arizona College of Public Health, Tucson, AZ.

lections is an issue for the quality of homeopathy in clinical practice, but the proper scientific response should be to seek ways to improve clinical practice through research (e.g., to seek objective physiologic and patient-centered trait predictors of future responsiveness<sup>11</sup>), rather than to discard the field as a whole.

Third, the Shang et al. paper is methodologically flawed even within the allopathic framework (see Aickin [pp. 755–757] in this issue). Therefore, logically, the Shang et al.<sup>2</sup> paper is not the final word on the entire research literature on homeopathy. In other areas of medical research, the notion that any paper—especially one meta-analysis of selected clinical studies—offers the final word on a topic is usually treated as scientifically risky if not unfair, illogical, and irrational.<sup>12</sup> As outlined below, there are many studies in the basic science, preclinical, and clinical literatures suggesting that homeopathically prepared remedies are not inert and that homeopathic care as an intervention is safe and effective for many patients. Apparently, *The Lancet's* view is that the conservative interpretation of a single review of only some of the “evidence” is unnecessary when the topic is homeopathic research.

Fourth, meta-analyses, even good ones, rely on quality ratings of internal validity of randomized controlled trials designed to test conventional drugs with specific effects on specific disease mechanisms.<sup>13</sup> No quality ratings of the homeopathy used in each study, such as ecologic validity, were used in the Shang et al. meta-analysis.<sup>2</sup> (Was homeopathic treatment provided in a clinically typical methodology? Were the outcomes of homeopathy in the study based on the prescribing skills of a single homeopath or of multiple well-qualified homeopaths? Were the homeopaths highly confident of their remedy selections? Were typical global and multiple local homeopathic outcomes systematically assessed in the study?) That is, “high quality” studies were judged solely in terms of their conventional strengths in testing a given intervention (i.e., homeopathy), as though it were a biomedical drug with a disease-specific action.

### PLAYING BY THE RULES: WHOSE RULES?

In terms of external validity, the fundamental principles of homeopathy are that the treatment addresses the patient's entire pattern of problems at once in a patient-specific but not disease-specific manner.<sup>14</sup> Homeopathic outcomes are different from those in conventional medicine; homeopaths report global and hierarchically organized multiple, multi-dimensional changes at local (body part) levels.<sup>14,15</sup> Thus the very nature of homeopathy, similar to another complex whole system of complementary and alternative medicine (CAM), acupuncture,<sup>16–19</sup> is inherently nonspecific. Nonspecific does not mean biologically inert; that is, nonspecificity is more than a simple “placebo” effect.<sup>20</sup> Shang et al.<sup>2</sup> stated in their methods section that they randomly chose only

one outcome from each study for their analysis if multiple outcomes were reported. By itself, this methodological error weakens the fairness of the comparisons between the homeopathic and allopathic studies. To infer from the data that homeopathic remedies do not exert disease-specific effects (i.e., that they are not allopathic drugs) is consistent with the claims of homeopathic clinicians and the conceptual principles of the field; but such a conclusion only highlights the need to design clinical studies of homeopathy that reflect the philosophical underpinnings and clinical practices of homeopathy rather than those of allopathy.

An analogy for a conventional drug would be to test the effects of penicillin for all patients with symptoms and signs of an apparent infection. The design quality of the studies would otherwise be excellent. However, penicillin will not work for patients with viral infections or bacterial infections that are resistant to its effects or for persons with fevers from other, noninfectious causes. Thus this drug might show benefit only for a subset of patients with symptoms of infections (i.e., the ones with true penicillin-sensitive infections). How would penicillin fare in a meta-analysis of studies averaging all patients together, evaluating only internal but not external ecologic or population validity, and ignoring the intrinsic nature of penicillin in benefiting certain patients? Variable luck of the investigators in recruiting patients with penicillin-sensitive infections in a given study as well as publication bias in medicine generally to favor publication of positive rather than negative results would likely lead to a current scenario from the Shang et al.<sup>2</sup> paper—that is, the publication of a small number of “high quality” positive studies but the rejection of penicillin for treatment of infections in general on the basis of the meta-analysis. Proponents would insist that penicillin is nonetheless very helpful for certain patients with the “right” infections and skeptics would scoff at the argument. But the proponents would be correct: penicillin is very helpful, but only for patients in a target population whose disease conditions match the capacity of the drug to act for them.<sup>21,22</sup> Thus, goes the situation for homeopathy.

In short, conventional mainstream medicine has defined the game, the rules, and the interpretation. At a practical level, the antipathy toward homeopathy in the clinical research funding world and the historical focus of homeopaths on clinical care have combined to leave homeopathic research without a sufficient number of funded investigators and with a research approach in only the earliest stages of development.<sup>22</sup> Those researchers who have performed homeopathic clinical studies have consciously or unwittingly agreed to evaluate their field by allopathic rather than homeopathic rules.

What if allopathic drugs were held to the non-disease-specific outcome standards routinely reported in homeopathy? Would allopathically treated patients, like homeopathically treated patients, report better overall well-being, greater energy, and improvement in multiple symptoms

(some of which they had forgotten to mention), with shifts in multiple mental, emotional, and physical problems toward recovery from a single agent with minimal side-effects and low cost? Does allopathy mobilize the same patterns of patient-wide, whole system changes that homeopaths report?<sup>23</sup> Future studies comparing homeopathy with allopathy need to level the playing field by evaluating for outcomes from both an allopathic and a whole-systems,<sup>24–26</sup> homeopathic point of view.<sup>27</sup>

### THE EVIDENCE BEYOND SHANG ET AL.

The *Lancet* editorial<sup>3</sup> expresses the usual opinion of skeptics that homeopathy is “absurd” because of the dilution factor of some of its medicines (remedies) beyond the Avogadro number (i.e., it must follow that remedies are biologically inert in living organisms). This is an opinion that is without supporting evidence. This editorial ignores the fact that homeopathic remedies are prepared not only with dilution but also with vigorous shaking or succussion. The basic science data suggest that it is the succussion that makes a key difference between an active versus an inactive agent in homeopathy. The actual replicated basic science systematic evidence from different, independent laboratories is that homeopathically prepared remedies beyond the Avogadro number differ from remedy-free solvent controls in their measurable properties, including calorimetry,<sup>28,29</sup> thermoluminescence,<sup>30</sup> and optical emission characteristics.<sup>31</sup> The findings challenge the assumptions of high-school chemistry, but not those of modern materials science.\* Prior research suggests that homeopathic basic science studies are prone to contaminants and confounds for which careful rigorous controls are needed<sup>32</sup> but not that the remedies are inert.

Moreover, the preclinical evidence from multiple different, independent laboratories is that homeopathically prepared remedies have biologically measurable effects both in *in vitro* and *in vivo* animal studies.<sup>33–36</sup> For example, the famous controversial Benveniste<sup>37</sup> paper in *Nature* showing ultradilutions of immunoglobulin E antiserum–modulated basophil histamine release<sup>38</sup> was promptly attacked via evaluation by a “quackbuster” magician and his colleagues. A recently published European multisite study with improved objective technology has now demonstrated that ultradilutions of histamine do modulate basophil activation.<sup>39</sup> *The Lancet’s* editorial<sup>3</sup> and Vandenbroucke<sup>4</sup> commentary made no mention of this fact.

In addition, laboratories in many different countries have demonstrated that homeopathically prepared remedies exert measurable effects in animals.<sup>35,36</sup> In isopathic research, an-

imals experimentally poisoned with arsenic show greater ameliorating effects on biologic toxicity under treatment with homeopathically prepared (diluted and succussed) arsenic than with placebo controls.<sup>40–43</sup> Homeopathically prepared glutamate has protective effects for rat neurons in cell culture when used isopathically for experimental glutamate toxicity.<sup>44</sup> Sleep electroencephalographic patterns of animals differ from controls after ingestion of one of two different homeopathically prepared remedies (i.e., *Coffea cruda*,<sup>45</sup> and *Nux vomica*<sup>46,47</sup> that are reported to exert effects on human sleep in clinical settings. Cataleptic effects of haloperidol increase as a function of concomitant treatment with ultra dilutions of various homeopathically prepared remedies in animals.<sup>48</sup> Ultradilute acetylsalicylic acid produces significant differences from controls in a laser-induced thrombus formation model system.<sup>49,50</sup> *In vitro* and *in vivo* animal study effects do not necessarily translate into clinical efficacy but they do indicate that homeopathic remedies are active agents.

Even the highly touted “negative” clinical study on dust mites prepared as a homeopathic remedy but prescribed isopathically, not homeopathically (i.e., not in accordance with actual homeopathic practice) to adults with asthma demonstrated different dynamic patterns of global disease, lung function, and mood responses to the verum remedy compared to the placebo.<sup>51</sup> Homeopathically prepared dust mite, prescribed isopathically in the latter study, did not act in the same manner as did the placebo.<sup>52</sup> Skeptics can rush to judgment that the net lack of clinical benefit in the study justifies rejection of the field of “homeopathy” (actually, by logic, this lack may support rejection of the clinical intervention of isopathy with dust mite in adult asthma, but offers no data on the field of homeopathic treatment per se), or open-minded scientists can look at the nonlinear dynamic findings from the remedy and wonder why.<sup>53</sup> Moreover, this laboratory has shown that verum individualized homeopathic remedies in fibromyalgia patients produce electroencephalographic pattern changes not seen with placebo under double-blinded conditions.<sup>54,55</sup> In short, the evidence is that homeopathically prepared remedies exert nonlinear dynamic effects on organisms different from those of conventional drugs. *The Lancet* editors<sup>3</sup> are willing to end homeopathy on the basis of the conclusions of a single flawed meta-analysis paper<sup>2</sup> that concludes a publication bias within a highly selected subset of the clinical literature but that overlooks the far larger body of scientific evidence suggesting that homeopathic remedies exert effects different from those of placebo.

The clinical evidence from numerous observational studies on hundreds to thousands of patients in different countries has consistently demonstrated that homeopathy benefits the majority of patients who receive it for a wide range of conditions and shows an excellent safety record.<sup>56–66</sup> In some studies<sup>57,64</sup> although not all,<sup>66</sup> homeopathy also generates significant cost savings via reduction in reliance on

\*Roy R, Tiller W, Bell IR. The structure of water: The materials science perspective. (Submitted for publication.)

conventional symptomatic drugs. When conventional medical researchers discuss conventional drugs, these scientists now argue that well-done observational studies have validity in the world of evidence<sup>13,67</sup> (e.g., in journals as prestigious as *The New England Journal of Medicine*<sup>68</sup>). A central point is that observational data in conventional medicine are often more relevant to effectiveness in everyday clinical practice (external ecologic validity) than are the randomized controlled trial (RCT) efficacy studies that focus on idealized replicable drug testing in uncomplicated patients (internal validity). However, in view of the fact that the observational data on homeopathy are consistently favorable to the field, mainstream skeptics would dismiss the body of observational findings in homeopathy as an inferior and unimportant form of data.

The Shang et al. paper<sup>2</sup> also made no comparison of safety issues. In the allopathic world, the evidence shows that even correctly prescribed conventional medications cause extensive morbidity and mortality<sup>69</sup> (although the extent of the latter findings also have been challenged as a flawed meta-analysis.<sup>70</sup> In the face of such data, it is inaccurate, and potentially harmful to patients seeking options, to conclude that allopathic medicine has been demonstrated to be superior to other forms of care,<sup>4</sup> especially complex systems with long historical traditions of benefit and safety.

### INDIVIDUAL DIFFERENCE FACTORS IN CLINICAL OUTCOMES RESEARCH

Is homeopathy some sort of panacea for all patients with all types of problems? Of course not. The evidence suggests that certain individuals are more inclined to use homeopathy (and other systems of CAM).<sup>71</sup> Initial data also indicate that some individuals with particular electroencephalographic responses to the first test dose of a remedy may be more likely to benefit.<sup>11</sup> The individual differences may stem more from the nature of the person such as genetically based personality traits<sup>71,72</sup> and accuracy of the pattern matching between the remedy and the unique symptomatology of the patient,<sup>14,73</sup> than the nature of the allopathic disease label. Patient recruitment in homeopathy studies following the conventional design model for pharmaceutical RCTs draws from the general pool of patients with a given disease label without regard to the target population of patients with a preference for and a capacity to respond to homeopathy. Few RCTs on homeopathy to date have recruited and then randomized the subset of potential responder patients<sup>21,22,73</sup> to active versus placebo groups. Potential responders might be prescreened, for example, by both personality tests<sup>72</sup> and electrophysiological testing<sup>11</sup> before randomized treatment.

Thus, the evidence indicates that the subject selection procedures of allopathically designed RCTs of homeopathy are a potentially inaccurate reflection of the real-world clinical

population of persons who end up in homeopathic treatment. The proper question is not a broad public health policy question that an RCT can answer<sup>12</sup> (i.e., does homeopathy work for everyone with a specific allopathic diagnosis *on average*?). Rather, the proper question is patient-centered at an *individual* level (i.e., is homeopathic treatment more effective than placebo in a specific patient who has the testable, prescreened potential to respond?).<sup>73</sup>

As consumer interest in complementary and alternative medicine continues to grow,<sup>74</sup> mainstream medicine has demanded that CAM researchers provide evidence for specific efficacy (where conventional drugs shine), with a secondary emphasis on safety, cost, or effectiveness data (where CAM may have its greatest advantages). At face value, evidence-based medicine is a reasonable and desirable goal for practice. Basing clinical care solely upon “expert” opinion and bias is fraught with potential risk of using ineffective or dangerous therapies.

The problem with evidence-based medicine derives not from the ideal definition and intent but rather from the actual application of the concept. Evidence-based medicine is defined as “the judicious use of the best current evidence in making decisions about the care of the individual patient. Evidence-based medicine (EBM) is meant to integrate clinical expertise with the best available research evidence and patient values.”<sup>75</sup> A large convergent body of research literature suggests that mainstream clinical practice itself does not live up to expectations in terms of RCT-derived, “evidence-based” efficacy standards.<sup>76–84</sup>

Research has shown that conventional physicians in practice or in training often cannot and do not follow evidence-based practice recommendations in the real world. Physicians report that they cannot determine from reading studies on large groups of patients with no comorbidity or who are taking concomitant drugs when and how the average findings from an idealized efficacy study on a single drug might apply to the specific, typically complicated individual patients who are consulting them. Logistical issues, dosage adjustments for side-effects, comorbid conditions, potential drug–drug interactions in polypharmacy, patient preferences and cultural beliefs, pharmaceutical company influences on patients and physicians, economic considerations, patient access and adherence, patient–provider relationships, and numerous other factors converge to determine the effectiveness of a treatment in real-world practice. The practical test of the value of an intervention for an individual patient is in its effectiveness as practiced in full context, not in efficacy-based RCT studies.

### CONCLUSIONS

Overall, as several investigators have commented, conventional medicine itself needs a much more extensive research literature on individualized treatment planning and on individual differences in response to treatment, to fill out

a more usable and rational evidence base to guide patient care.<sup>85</sup> Homeopathy, as a complex intervention, has important lessons to teach clinicians and researchers with regard to issues in individualized treatment, patterns of outcomes, and even the nonlinear dynamic processes of healing in the patient as a whole system.<sup>15,86</sup> The body of scientific evidence on homeopathy extends far beyond the limitations of the Shang et al.<sup>2</sup> study. The data in the literature show that a number of curious—and sometimes clinically beneficial—phenomena can occur during homeopathic treatment.<sup>24</sup> It behooves the medical and scientific community to reassess its biases and to look in a far more balanced and thoughtful way at all of the evidence.<sup>12,87,88</sup>

### ACKNOWLEDGMENTS

This work was supported in part by National Institutes of Health/National Center for Complementary and Alternative Medicine grants K24 AT00057 and R21 AT001319.

### REFERENCES

- Orwell G. *Animal Farm*. New York, NY: Harcourt Brace Jovanovich, 1946.
- Shang A, Huwiler-Muntener K, Nartey L, et al. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *Lancet* 2005;66:726–732.
- The Lancet. The end of homeopathy. *Lancet* 2005;366:690.
- Vandenbroucke JP. Homeopathy and “the growth of truth.” *Lancet* 2005;366:691–692.
- Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. *Ann Intern Med* 2001;134:663–694.
- Cucherat M, Haugh MC, Gooch M, et al. Evidence of clinical efficacy of homeopathy: A meta-analysis of clinical trials. HMRAG. Homeopathic Medicines Research Advisory Group. *Eur J Clin Pharmacol* 2000;56:27–33.
- Linde K, Clausius N, Ramirez G, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997;350:834–843.
- Reilly D, Taylor MA, Beattie NG, et al. Is evidence for homeopathy reproducible? [see comments]. *Lancet* 1994;344:1601–1606.
- Hahnemann S. *Organon of the Medical Art*, 6th ed. O’Reilly WB, Decker S, eds. Redmond, WA: Birdcage Books, 1843.
- Bell IR, Lewis DAI, Brooks AJ, et al. Improved clinical status in fibromyalgia patients treated with individualized homeopathic remedies versus placebo. *Rheumatology* 2004;43:577–582.
- Bell IR, Lewis DAI, Schwartz GE, et al. Electroencephalographic cordance patterns distinguish exceptional clinical responders with fibromyalgia to individualized homeopathic medicines. *J Altern Complement Med* 2004;10:285–299.
- Jonas WB. The evidence house: How to build an inclusive base for complementary medicine. *West J Med* 2001;175:79–80.
- Concato J, Horwitz RI. Beyond randomised versus observational studies. *Lancet* 2004;363:1660–1661.
- Vithoulkas G. *The Science of Homeopathy*. New York: Grove Weidenfeld, 1980.
- Bell IR, Baldwin CM, Schwartz GE. Translating a nonlinear systems theory model for homeopathy into empirical tests. *Altern Ther Health Med* 2002;8:58–66.
- Gould A, MacPherson H. Patient perspectives on outcomes after treatment with acupuncture. *J Altern Complement Med* 2001;7:261–268.
- Paterson C, Britten N. Acupuncture for people with chronic illness: Combining qualitative and quantitative outcome assessment. *J Altern Compl Med* 2003;9:671–681.
- Paterson C, Dieppe P. Characteristic and incidental (placebo) effects in complex interventions such as acupuncture. *BMJ* 2005;330:1202–1205.
- Schulman D. The unexpected outcomes of acupuncture: Case reports in support of refocusing research designs. *J Altern Complement Med* 2004;10:785–789.
- Walach H. The efficacy paradox in randomized controlled trials of CAM and elsewhere: Beware of the placebo trap. *J Altern Complement Med* 2001;7:213–218.
- Caspi O, Bell IR. One size does not fit all: Aptitude–treatment interaction (ATI) as a conceptual framework for outcome research: Part I. What is ATI research? *J Altern Complement Med* 2004;10:580–586.
- Caspi O, Bell IR. One size does not fit all: Aptitude–treatment interaction (ATI) as a conceptual framework for outcome research: Part II. Research designs and their application. *J Altern Complement Med* 2004;10:698–705.
- Bell IR, Koithan M, Gorman MM, Baldwin CM. Homeopathic practitioner views of changes in patients undergoing constitutional treatment for chronic disease. *J Altern Complement Med* 2003;9:39–50.
- Ritenbaugh C, Verhoef M, Fleishman S, et al. Whole systems research: A discipline for studying complementary and alternative medicine. *Altern Ther Health Med* 2003;9:32–46.
- Verhoef M, Lewith G, Ritenbaugh C, et al. Whole systems research: Moving forward. *Focus Altern Complement Ther* 2004;9:87–90.
- Verhoef MJ, Lewith G, Ritenbaugh C, et al. Complementary and alternative medicine whole systems research: Beyond identification of inadequacies of the RCT. *Complement Ther Med* 2005;13:206–212.
- Bell IR. Evidence-based homeopathy: Empirical questions and methodological considerations for homeopathic clinical research. *Am J Homeopath Med* 2003;96:17–31.
- Elia V, Niccoli M. New physico-chemical properties of extremely diluted aqueous solutions. *J Therm Anal Calorimetry* 2004;75:815–836.
- Elia V, Niccoli M. Thermodynamics of extremely diluted aqueous solutions. *Ann N Y Acad Sci* 1999;879:241–248.
- Rey L. Thermoluminescence of ultra-high dilutions of lithium chloride and sodium chloride. *Physica A* 2003;323:67–74.
- Bell IR, Lewis D, Brooks AJ, et al. Gas discharge visualization evaluation of ultramolecular doses of homeopathic medicines under blinded, controlled conditions. *J Altern Complement Med* 2003;9:25–38.

32. Becker-Witt C, Weibhuhn TER, Ludtke R, Willich SN. Quality assessment of physical research in homeopathy. *J Altern Complement Med* 2003;9:113–132.
33. Bellavite P, Signorini, A. *The Emerging Science of Homeopathy: Complexity, Biodynamics, and Nanopharmacology*, 2nd ed. Berkeley: North Atlantic Books, 2002.
34. Bertani S, Lussignoli S, Andrioli G, et al. Dual effects of a homeopathic mineral complex on carrageenan-induced oedema in rats. *Br Homoeopath J* 1999;88:101–105.
35. Endler PC, Schulte, J, ed. *Ultra High Dilution. Physiology and Physics*. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1994.
36. Schulte J, Endler PC, eds. *Fundamental Research in Ultra High Dilution and Homoeopathy* Dordrecht. The Netherlands: Kluwer Academic Publishers, 1998.
37. Benveniste J, Ducot B, Spira A. Memory of water revisited. *Nature* 1994;370:322.
38. Davenas E, Beauvais F, Amara J, et al. Human basophil degranulation triggered by very dilute antiserum against IgE. *Nature* 1988;333:816–818.
39. Belon P, Cumps J, Ennis M, et al. Histamine dilutions modulate basophil activation. *Inflamm Res* 2004;53:181–188.
40. Datta S, Mallick P, Bukhsh AR. Efficacy of a potentized homeopathic drug (Arsenicum Album-30) in reducing genotoxic effects produced by arsenic trioxide in mice: II. Comparative efficacy of an antibiotic, actinomycin D alone and in combination with either of two microdoses. *Complement Ther Med* 1999;7:156–163.
41. Kundu SN, Mitra K, Khuda Bukhsh AR. Efficacy of a potentized homeopathic drug (Arsenicum-Aalbum-30) in reducing cytotoxic effects produced by arsenic trioxide in mice: IV. Pathological changes, protein profiles, and content of DNA and RNA. *Complement Ther Med* 2000;8:157–165.
42. Mallick P, Chakrabarti MJ, Guha B, et al. Ameliorating effect of microdoses of a potentized homeopathic drug, *Arsenicum album*, on arsenic-induced toxicity in mice. *BMC Complement Altern Med* 2003;3(7). Online document at [www.biomedcentral.com/1472-6882/3/7](http://www.biomedcentral.com/1472-6882/3/7) Accessed October 17, 2005.
43. Mitra K, Kundu SN, Khuda Bukhsh AR. Efficacy of a potentized homeopathic drug (Arsenicum Album-30) in reducing toxic effects produced by arsenic trioxide in mice: II. On alterations in body weight, tissue weight and total protein. *Complement Ther Med* 1999;7:24–34.
44. Jonas W, Lin Y, Tortella F. Neuroprotection from glutamate toxicity with ultra-low dose glutamate. *Neuroreport* 2001; 12:335–339.
45. Ruiz-Vega G, Perez-Ordaz L, Proa-Flores P, et al. An evaluation of *Coffea cruda* effect on rats. *Br Hom J* 2000;89: 122–126.
46. Ruiz G, Torres JL. Homeopathic effect on the sleep pattern of rats. *Br Hom J* 1997;86:201–206.
47. Sukul A, Sinhabau SP, Sukul NC. Reduction of alcohol induced sleep time in albino mice by potentized *Nux vomica* prepared with 90% ethanol. *Br Hom J* 1999;88:58–61.
48. Sukul NC, Bala SK, Bhattacharyya B. Prolonged cataleptogenic effects of potentized homeopathic drugs. *Psychopharmacology* 1986;89:338–339.
49. Belougne-Malfatti E, Aguejouf O, Doutremepuich F, et al. Combination of two doses of acetyl salicylic acid: Experimental study of arterial thrombosis. *Thromb Res* 1998;90:215–221.
50. Doutremepuich C, Aguejouf O, Pintigny D, et al. Thrombogenic properties of ultra-low-dose of acetylsalicylic acid in a vessel model of laser-induced thrombus formation. *Thromb Res* 1994;76:225–229.
51. Lewith GT, Watkins AD, Hyland ME, et al. Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite: Double blind randomised controlled clinical trial. *BMJ* 2002;324:520–523.
52. Hyland ME, Lewith GT. Oscillatory effects in a homeopathic clinical trial: An explanation using complexity theory, and implications for clinical practice. *Homeopathy* 2002;91:145–149.
53. Bellavite P. Complexity science and homeopathy: A synthetic overview. *Homeopathy* 2003;92:203–212.
54. Bell IR, Lewis DA 2nd, Schwartz GE, et al. Electroencephalographic cordance patterns distinguish exceptional clinical responders with fibromyalgia to individualized homeopathic medicines. *J Altern Complement Med* 2004;10:285–299.
55. Bell IR, Lewis DAI, Lewis SE, et al. Electroencephalographic alpha sensitization in individualized homeopathic treatment of fibromyalgia. *Int J Neurosci* 2004;114:1195–1220.
56. Anelli M, Scheepers L, Sermeus G, et al. Homeopathy and health related quality of life: A survey in six European countries. *Homeopathy* 2002;91:18–21.
57. Frenkel M, Hermoni D. Effects of homeopathic intervention on medication consumption in atopic and allergic disorders. *Altern Ther Health Med* 2002;8:76–79.
58. Goldstein MS, Glik D. Use of and satisfaction with homeopathy in a patient population. *Altern Ther Health Med* 1998;4:60–65.
59. Guthlin C, Lange O, Walach H. Measuring the effects of acupuncture and homeopathy in general practice: An uncontrolled prospective documentation approach. *BMC Public Health* 2004;4:6. Online document at [www.biomed](http://www.biomed)
60. Mathie RT. Clinical outcomes research: contributions to the evidence base for homeopathy. *Homeopathy* 2003;92:56–57.
61. Riley D, Fischer M, Singh B, et al. Homeopathy and conventional medicine: An outcomes study comparing effectiveness in a primary care setting. *J Altern Compl Med* 2001;7: 149–159.
62. Schlappack O. Homeopathic treatment of radiation-induced itching in breast cancer patients: A prospective observational study. *Homeopathy* 2004;93:210–215.
63. Thompson EA, Reilly D. The homeopathic approach to symptom control in the cancer patient: A prospective observational study. *Palliat Med* 2002;16:227–233.
64. Van Wassenhoven M, Ives G. An observational study of patients receiving homeopathic treatment. *Homeopathy* 2004;93:3–11.
65. Walach H, Guthlin C. Effects of acupuncture and homeopathy: Prospective documentation. Interim results. *Br Hom J* 2000;89(suppl 1):S31–S34.
66. Witt C, Keil T, Selim D, et al. Outcome and costs of homeopathic and conventional treatment strategies: A comparative cohort study in patients with chronic disorders. *Complement Ther Med* 2005;13:79–86.
67. Concato J. Observational versus experimental studies: What's the evidence for a hierarchy? *NeuroRx* 2004;1:341–347.
68. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *NEJM* 2000;342:1887–1892.

69. Kvasz M, Allen IE, Gordon MJ, et al. Adverse drug reactions in hospitalized patients: A critique of a meta-analysis. *Med-GenMed* 2000;2:E3 Accessed October 17, 2005.
70. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. *JAMA* 1998;279:1200–1205.
71. Honda K, Jacobson JS. Use of complementary and alternative medicine among United States adults: The influences of personality, coping strategies, and social support. *Prev Med* 2005;40:46–53.
72. Bell IR, Lewis DAI, Brooks AJ, et al. Individual differences in response to randomly assigned active individualized homeopathic and placebo treatment in fibromyalgia: Implications of a double-blind optional crossover design. *J Altern Complement Med* 2004;10:269–283.
73. Frei H, Everts R, von Ammon K, et al. Homeopathic treatment of children with attention deficit hyperactivity disorder: A randomised, double blind, placebo controlled crossover trial. *Eur J Pediatr* 2005 (Epub ahead of print).
74. Barnes PM, Powell-Griner E, McFann K, et al. Complementary and Alternative Medicine Use among adults: United States, 2002. Hyattsville, MD: National Center for Health Statistics. *Adv Data* 2004;343:1–19.
75. Online document at: [www.medterms.com/script/main/art.asp?articlekey=33300](http://www.medterms.com/script/main/art.asp?articlekey=33300) Accessed September 9, 2005.
76. Avorn J, Chen M, Hartley R. Scientific versus commercial sources of influence on the prescribing behavior of physicians. *Am J Med* 1982;73:4–8.
77. Bates DW, Kuperman GJ, Wang S, et al. Ten commandments for effective clinical decision support: Making the practice of evidence-based medicine a reality. *J Am Med Inform Assoc* 2003;10:523–530.
78. Chren MM, Landefeld CS. Physicians' behavior and their interactions with drug companies: A controlled study of physicians who requested additions to a hospital drug formulary. *JAMA* 1994;271:684–689.
79. Fisher MA. Physicians and the pharmaceutical industry: A dysfunctional relationship. *Perspect Biol Med* 2003;46:254–272.
80. Freeman AC, Sweeney K. Why general practitioners do not implement evidence: Qualitative study. *BMJ* 2001;323:1100–1102.
81. Green ML, Ruff TR. Why do residents fail to answer their clinical questions? A qualitative study of barriers to practicing evidence-based medicine. *Acad Med* 2005;80:176–182.
82. Kravitz RL, Epstein RM, Feldman MD, et al. Influence of patients' requests for direct-to-consumer advertised antidepressants: A randomized controlled trial [see comment]. *JAMA* 1995;293:1995–2002.
83. Rosenbloom ST, Giuse NB, Jerome RN, et al. Providing evidence-based answers to complex clinical questions: Evaluating the consistency of article selection. *Acad Med* 2005;80:109–114.
84. Wazana A. Physicians and the pharmaceutical industry: Is a gift ever just a gift? [see comments]. *JAMA* 2000;283:373–380.
85. August GJ, Winters KC, Realmuto GM, et al. Moving evidence-based drug abuse prevention programs from basic science to practice: "Bridging the efficacy-effectiveness interface" [Review]. *Subst Use Misuse* 2004;39(10–12):2017–2053.
86. Hyland M. Extended network generalized entanglement theory: Therapeutic mechanisms, empirical predictions, and investigations. *J Altern Complement Med* 2003;9:919–936.
87. Caulfield T, DeBow S. A systematic review of how homeopathy is represented in conventional and CAM peer reviewed journals. *BMC Complement Altern Med* 2005;5:12. Online document at [www.biomedcentral.com/1472-6882/5/12](http://www.biomedcentral.com/1472-6882/5/12) Accessed October 17, 2005.
88. Barber B. Resistance by scientists to scientific discovery. *Science* 1961;134:596–602.

Address reprint requests to:

*Iris R. Bell, M.D., M.D.(H.), Ph.D.*

*The University of Arizona College of Medicine*

*1501 North Campbell Avenue, MS 245153*

*Tucson, AZ 85724-5153*

*E-mail: [ibell@u.arizona.edu](mailto:ibell@u.arizona.edu)*