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THE HOMEOPATHY DEBATE

HORTON DEPLORES BREACH; AS DO WE HIS

Dear Editor:

We read with interest Richard Horton's, letter in *The Times* on Monday August 29th concerning Professor Ernst leaking a confidential report produced for the Prince of Wales's Foundation for Integrated Health.[1] To quote Horton: "Professor Ernst seems to have broken every professional code of scientific behaviour by disclosing correspondence referring to a document that is in the process of being reviewed and revised prior to publication. This breach of confidence is to be deplored."[1]

We completely agree with him. Is it not, we ask, a similar breach of confidence to leak substantive information from a World Health Organisation Report on Homeopathy, while it is still in the process of drafting and peer review, and then to use these details to critique homeopathy?[2]

We are particularly concerned, as clearly is Dr. Richard Horton, about maintaining the security of the peer-review process. We find it extraordinary, even though we submitted this letter in good time, that Dr. Horton has chosen not to publish it. At the center of a healthy academic environment is the capacity and freedom to enter into robust and well-informed academic debate. This does not appear to be happening in relation to our letter and the response that we have had from *The Lancet*.

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SHANG ET AL. CARELESSNESS, COLLUSION, OR CONSPIRACY?

Dear Editor:

Confusion, gradually turning into outrage, reigned in the days following the Lancet's publication of Shang et al.'s meta-analysis of homeopathy research.[1] Even now, doubts about which studies were involved are making these authors' work nigh impossible to reanalyze. Yet, even if we were to put up a reasoned defense, the statistical issues would prove too complicated for the media's fleeting attention span. And a lot of media attention will be needed to heal wounded public and professional confidence in homeopathy, for the damage wrought by *The Lancet*'s grandstanding is real, and there will be much glee in "pharma-co" head offices now that the sound-bite "scientists have proven homeopathy doesn't work" is in circulation. Though homeopathy is resilient, it will take more than a few polite letters in *The Lancet* to limit the damage—perhaps especially to homeopathy's credibility with doctors.

In parallel with Shang et al.'s Swiss-based study, the Swiss government had announced impending cuts in state insurance reimbursement for homeopathy.[2] Conspiracy theorists will no doubt see the Shang Et Al. Affair as the thin end of a carefully crafted wedge; and, with the tips of ever more adverse-event icebergs threatening to sink "pharma-cartels" in an ocean of punitive damages, as a useful diversionary tactic. Evidence-based medicine as a propaganda weapon; as marketing? Certainly. Richard Smith, ex-editor of the *British Medical Journal,* has recently revealed just how—and how often—the cartels use heavily spun research results in peer-reviewed journals to make shop windows for their products.[3]

Attacking complementary and alternative medicine—especially in the late-summer slow-news season when it can

make headlines in the *Times*—may be an effective smokescreen. And this illustrates how skillful timing can make an international media splash possible when vested interests, a certain kind of research, and editorial bias come together. Can we create as big a splash now that the failings of Shang et al.'s study are becoming clearer? It is easy enough to infer bad faith at work in its sampling, interpretation of data, and path to publication. What the media will be more interested in is whether the author's omissions were carelessness or conspiracy and just why *The Lancet* was suckered into such editorial bias, and—to its shame—treated the study's publication as though it was a celebrity wedding in *Hello* magazine. This is not for the first time either: Back in 1990 *The Lancet* published a paper by Bagenal et al. (a.k.a. the Chilvers Report) on outcomes at the Bristol Cancer Help Centre (BCHC; Bristol, UK). This patently flawed study was exploded into the media by the same journal—with the direct result that BCHC all but sank without a trace. The Director of the Imperial Cancer Research Fund (responsible for the study) Walter Bodmer later admitted its failings[5] but the public only heard the bang, not the whimper.

Shang et al.'s study is full of holes but will take more than a retraction from *The Lancet* to get the new message out. The parallels with Bristol are worrying. Whither homeopathy goest unless media power can be brought to bear on this situation?

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BIAS IN THE TRIAL AND REPORTING OF TRIALS OF HOMEOPATHY: A FUNDAMENTAL BREAKDOWN IN PEER REVIEW AND STANDARDS?

Dear Editor:

In late August, an article by Shang et al.[1] appeared in *The Lancet* suggesting that homeopathy is comparable to placebo and should therefore be omitted from the physician's armamentarium. We were astonished that this paper passed *The Lancet*'s peer review. We would like to reveal the problems and explain some of the fundamental errors in this publication.

First, we have to accept that homeopathy is not a protected word. The problem is that it may be used equally by homeopathically trained professionals as well as by nonprofessionals. Therefore, training is mandatory in order to understand the basics of homeopathy. While the main principle underlying the science of homeopathy is the "Law of Similars," most nonhomeopaths believe that potentization is the underlying main principle. However, administration of digitalis for certain cardiac and other physiological indications is a homeopathic action whether the prescriber is a homeopath or not. Of course, people who have knowledge of homeopathy have seen that potentized remedies may act in a deeper way. While the reason for this phenomenon remains to be investigated and explained adequately, it should be made clear that homeopathy works also with nonpotentized remedies. This way, people who have an intellectual restriction regarding potentization are relieved and might find it easier to accept homeopathy.

Second, the phenomenon of placebo is far from solved: While it is amusing to observe earnest scientists suddenly switching from mere calculations and numbers to an esoteric term such as "placebo," believing in it like a religious dogma (Are the clinical effects of homoeopathy placebo effects?[1]), Hrobjartsson and Gotzsche[2] have published a paper which compels us to reconsider the role of the placebo: In 27 trials involving the treatment of pain, placebo had a beneficial effect (−0.27; 95 percent confidence interval [CI], −0.40 to −0.15). This corresponded to a reduction in the intensity of pain of 6.5 mm on a 100-mm visual-analogue scale. The authors found little evidence in general that placebos had powerful clinical effects. Although placebos had no significant effects on objective or binary outcomes, placebos had possible small benefits in studies with continuous subjective outcomes and for the treatment of pain. Outside the setting of clinical trials, there is no justification for the use of placebos.

Now we want to focus on the paper by Shang et al.[1] and to lead the reader through the paper so that he/she can easily find the errors without necessarily being scientists: Please look to the second part of the title "Comparative study of placebo-controlled trials of homoeopathy and allopathy." The problem is that it is not a "comparative study"; instead

it is just an investigation of two methods separately. Therefore, *the title does not meet the content of the paper*.

If you read the abstract, you will be astonished to find out that homeopathy works: Looking at the 110 studies of conventional medicine and the 110 studies of homeopathy, the statistics show a clear benefit for both methods (of course, in a separate investigation, the methods are in no way comparative!). Surprisingly, a less-pronounced heterogeneity for homeopathy trials as well as a higher quality of the investigated studies were found in the homeopathy group (19% versus 8%).

Let us make a trivial comparison: Coming from a small country, we always look with a degree of envy at our big neighbors. When the Austrian National Soccer team plays against the Germans, Austria usually loses. What is the mystery behind this reality? The number of inhabitants in Austria is approximately 8 million, in Germany it is approximately 80 million. Assuming that the people in both countries are equally interested in soccer and the number of active soccer players is a certain percentage of the number of inhabitants, there is a tenfold higher number of professionals to be expected in Germany by comparison with Austria. This means that the pool of first-class players is much larger in Germany and the coach has a much higher probability of finding a winning team. If, however, one looks at skiing, with the same proportion of inhabitants, the number of mountains and therefore skiers is much higher in Austria that in Germany. This explains why Austrian skiers have a relatively high success rate in competition by comparison.

With this example in mind, let us have a look again at the *Lancet* paper: The number of randomized clinical trials (RCTs) is approximately165 in homeopathy compared to $>$ 200,000 in conventional medicine. So, one would expect an obvious "victory" for conventional medicine. Surprisingly, a less-pronounced heterogeneity for homeopathy trials as well as a higher quality of the investigated studies was found in the homeopathy group (19% versus 8%). This suggests that the homeopaths are better "skiers"!

The question from nonhomeopaths is often why the number of homeopathic RCTs is so low. There are a number of answers: First, homeopathy is based on quality, which is difficult to evaluate compared to conventional medicine, which is based on quantity. If you perform homeopathy in a classic way, prescriptions are adjusted individually. This means that patients with the same "conventional" diagnosis may receive different potentized remedies. Second, large studies almost never allow a subtle individual prescription. Therefore, large studies are based on routine administration. Third, homeopaths are mostly working in private offices that do not readily allow for participation in a research studies. Fourth, there is almost no public and/or pharmaceutical support for studies. There are no universities with a special interest in homeopathy; funding agencies refuse to support homeopathic studies. Fifth, homeopaths are not used to RCTs like conventional physicians. Sixth, homeopaths are often not interested in RCTs.

Now we approach a point, which is usually a reason for immediate rejection of a paper in a peer-reviewed top journal: It is mandatory for the Summary or at least the Introduction to describe the aim of a study. In both sections of the *Lancet* paper by Shang er al., we have searched for this aim in vain.

There is a further flaw in the study: The authors wrote that, *after* having investigated each of the 110 studies of the two methods, these researchers then singled out "larger trials of higher quality." Please bear in mind that the design of the study does *not* allow a comparison between studies of homeopathy and studies of conventional medicine. However Shang et al., evaluated the specific effects of these two methods in two separate analyses. Surprisingly, and without citing the studies or references to them, these authors singled out 8 (homeopathic) versus 6 (conventional medicine) studies. Why 8 versus 6 and not 8 versus 9 or 12 versus 8? The answer may be found in the plots of Figure 2 of the paper by Shang[1] et al. We are almost sure that including just one or two more papers in the conventional medicine group would have affected the results crucially. From a professional statistician's point of view, the random selection of the 14 studies is a *post-festum hypothesis* but was not planned in the original design of the study. Therefore, we strongly suspect that the authors chose this second-line investigation because their predefined desired effect was not found in the first investigation. If it had been planned, why was it done *after* having investigated the initial 110 studies?

Even if the authors had chosen this predefined selection, there remain some uncertainties. When focusing on the 8 "larger trials of higher reported methodological quality," the odds ratio was 0.88 (CI 95%; 0.65–1.19) in homeopathy: While this result does not prove an effect of the study design at the 5% level, neither does it disprove the hypothesis that the results might have been achieved by homeopathy. In contrast, with conventional medicine, the odds ratio was 0.58 (CI 95%; 0.39–0.85), which indicates that the results may not be explained by mere chance with a 5% uncertainty.

Another problem arises with the drastic reduction from 220 to 14 studies. While the authors emphasize that the 110 versus 110 studies were matched, it is fairly unlikely that the 6 trials of conventional medicine were still matched to the 8 trials of homoeopathy. Yet, this is another point where the study results are flawed. There is no hint or mention of which studies were selected for these comparisons. As far as we can deduce, three of the studies were done with *Oscilliococcinum* and three with complex remedies. These 6 studies are in no way "homeopathic." We are sorry about that but offer to people interested in what constitutes homeopathy a free course in basic homeopathy at the Doctor's Association for Classical Homeopathy or the Austrian Society for Homeopathic Medicine.

Surprisingly, neither the actual data (odds ratio, matching parameters, etc.) nor a funnel plot (to indicate that there is no bias anymore) of these (only 14) trials are shown al-

though it was these parameters that constituted the grounds for the authors' and editors' widely reported conclusions.

Another weakness in the study concerns the questionable use of funnel plots. Funnel plots are believed to detect publication bias as well as heterogeneity and so enable detection of fundamental differences between studies. New evidence suggests that both of these common beliefs are seriously flawed.[3,4]

A further problem with the study concerns the fact that no indication is given as to at which level homeopathy would have become statistically significant. Furthermore, when dealing with such a controversial subject, the serious scientific community seeks rather to use the 1% level of statistical significance to determine effectiveness. At this level, the odds ratio for the conventional studies would not reach significance either. Moreover, the statistician fails even to specify the power of the test used in the study.

The authors admit that choosing a different sample of 8 trials would have yielded a positive result (e.g, the 8 trials on "acute infections of the upper respiratory tract," as mentioned in the Discussion section). However, the authors go on to state clearly in their Discussion that they are biased against homeopathy, assuming that it can not work in opposition to conventional medicine. How could such a team even begin an objective investigation? They state clearly their own bias at the outset!

In 2001, a paper in the *British Medical Journal* stated:

> The largest trials of homoeopathy (those with the smallest standard error) that were also double blind and had adequate concealment of randomisation show no effect. The evidence is thus compatible with the hypothesis that the clinical effects of homoeopathy are completely due to placebo and that the effects observed in Linde et al's meta¸analysis are explained by a combination of publication bias and inadequate methodological quality of trials. We emphasise, however, that these results cannot prove that the apparent benefits of homoeopathy are due to bias.[5]

One of the coauthors of that *British Medical Journal* paper was Mathias Egger [who contributed to the Shang et al. paper in *The Lancet*.[2]]

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FAILURE TO EXCLUDE FALSE NEGATIVE BIAS: A FUNDAMENTAL FLAW IN THE TRIAL OF SHANG ET AL.

Dear Editors:

The study by Shang et al.[1] does not support your headline of "the end of homeopathy." The study itself, while attempting to eliminate false positive bias in randomized placebo-controlled homeopathy trials (RCTs), introduces bias by failing to assess for false-negative bias. False-negative biases are omnipresent in RCTs but we argue that they are more likely in homeopathy.

- For example, in a pediatric RCT on respiratory infections, homeopathy was provided versus placebo *in addition* to standard antibiotic treatment and tonsillectomy.[2] Homeopathy had to prove *benefit additional* to conventional therapy, a difficult burden of proof. With homeopathy being effective, control patients would need more antibiotics and surgery, and did so in this study. Such a surplus of conventional therapies in control patients can easily compensate for homeopathy effects in verum patients and create false-negative results.
- False-negatives are induced when the basic simile principle of homeopathy is neglected and an identical single remedy given to all patients, making RCTs easier to perform. For example, a RCT on *Rhus tox.* with individualized simile matching produced a positive result.[3] A *Rhus tox*. RCT neglecting simile turned out to be negative.[4]
- Randomized trials have important limitations in complex treatment procedures that require particular skills[5]; homeopathy, especially classical homeopathy, is highly skill-dependent. Finding the correct homeopathic simile depends on indepth anamnesis in an atmosphere of trust, which is disrupted by randomization. Skilled practitioners with positive treatment experience are, for ethical reasons, less likely to participate in RCTs.

Other false-negative factors are: dropouts and noncompliers; contamination; informed consent; submissive answers; and insensitive questionnaires, group assimilations, conditioning, cognitive interactions, et cetera. In one study, several can be present. Assessing trial quality according to randomization, blinding, and size does not weed out trials with false-negative bias: "Orthodoxy always invokes the danger of Type One errors to ensure the occurrence of Type Two errors!" As Woods demonstrated, the logistics of large trials often need simplified protocols that easily lead to false-negative results.[6] Conditions necessary for quality homeopathy treatment, especially classical homeopathy are less likely to be provided in well-randomized, well-blinded, and large trials. Unfortunately, the authors refused our requests to identify the decisive 14 "larger trials of higher reported methodological quality."[1] This makes it impossible to assess if these larger trials allowed for optimal treatment conditions or if simplifications put homeopathy at a disadvantage.

Shang et al. interpreted asymmetric funnel plots as publication bias[1] but this warrants further proof: A 1997 meta-analysis on homeopathy[7] had dismissed publication bias after extensive inquiries with manufacturers, researchers, and practitioners. And, concerning more pronounced between-trial heterogeneity in conventional medicine, its greater diversity of treatment methods also has to be taken in account.

In conclusion, this meta-analysis by Shang et al. is far from confirmative and false-negative bias seems to have been the blind spot.

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UNDERSTANDING PLACEBO EFFECTS IN HOMEOPATHIC CLINICAL TRIALS

Dear Editor:

The paper of Shang et al. views homeopathy through the lens of a meta-analysis.[1] Aware of the limitations of this approach, they counsel that future research should be deflected away from placebo-controlled trials and toward understanding putative "context effects." We are just finishing a program of empirical work seeking to do exactly this.

We recruited 18 routine referrals to the Bristol Homeopathic Hospital (United Kingdom; National Health Service) living with one of three index conditions (eczema, chronic fatigue syndrom, or irritable bowel syndrome). Patients were interviewed before and after a course of five homeopathic consultations. All interviews and consultations were recorded and transcribed for qualitative data analysis.

Outcome was assessed by interview, artwork, generic and condition-specific numerical outcome measures, and reports from "significant others." Over an 8-month period, a third of the subjects experienced a significant health gain, a third some gain, and a third no gain. The main purpose of the study was to explore the "active ingredients" of the homeopathic approach in accordance with the Medical Research Council "Framework for design and evaluation of complex interventions to improve health."[2]

We failed to demonstrate "strong beliefs about the effectiveness of homeopathy" in this sample. Of the 18 subjects, 13 professed to have no prior understanding of what homeopathy was or how it worked. Only four had prior experience. They were driven primarily by persistent health problems that were not responding to conventional interventions. However an openess to the "mind–body" connection was found in all but one of the subjects with a major health gain, confirming findings in other contexts.[3]

It is often assumed that homeopathy works because homeopathic doctors are empathic. Using the CARE scale of Mercer, patients rated their doctors' empathy at around the average for general practitioners in Scotland.[4] In one case, there was poor empathy and a poor outcome but, otherwise, CARE ratings did not correlate (within this small sample) with outcomes. Empathy may be necessary but not sufficient for a good outcome.

Potentially therapeutic elements of the process included disclosure of previously unrevealed psychological trauma and the trend in homeopathy to listen in depth to somatic and psychological symptomatology and facilitate the patients' understanding of links between these domains. The matching of these predicaments with individualized remedies corresponds to indigenous healing practices across the world.[5]

However, while only indicative, our data are also consistent with a specific effect of remedy selection and administration. Higher homeopathicity (i.e., the accuracy of individualized remedy choices) was associated with better outcome. Health gains bore a temporal relationship to taking the remedies. Patient accounts clearly articulate phenomena traditionally associated with remedy action, such as aggravations and "proving" symptoms.

We conclude that homeopathy cannot be considered like any other pharmaceutical intervention because the approach is composed of a range of putative active ingredients that could mediate clinical effects that would not be revealed using placebo designs. The placebo effects referred to by Shang et al. are often specific to homeopathy, highly complex, and potentially dependent on the remedy selection and administration process.

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SIR: IS THAT BIAS?

Dear Editor:

This is a fascinating lesson in bias with useful examples for students.

Shang et al.[1] guide us to counter the biases of small-scale meta-analyses by "borrowing strength" from its larger context. So, before commenting on their small-scale data sets and interpretations, let me apply their teaching by summarizing their "big picture" result: In 110 trials each of conventional drugs and homeopathic drugs "most odds ratios indicated a beneficial intervention" (i.e., they both worked better than placebo). This fits previous large-scale meta-analyses of the limited homeopathic trial data set, it fits conventional research, and it fits impressions of many researchers with hands-on experience of both systems.

Next, the paper offers two key theoretical contributions about bias, with useful practical demonstrations. The first piece of theory: "detection of bias is difficult when meta-analyses are based on small numbers of trials." The first demonstration: two small numbers meta-analyses—will the student spot the biases? Is it biased to reject the very positive one (8 respiratory trials) because, well, because it is so positive—and so it "might promote the conclusion that the results cannot be trusted." Let's see, they teach that small-scale conclusions should "borrow strength" from the bigger surrounding picture and its confounding biases—"Please Sir, is it a bias that their *a priori* assumption was that homeopathy effects are due to nonspecific artefacts, and conventional effects are not?" "Quiet boy!"

Their second lesson in interpreting small-number meta-analyses illustrates their second theoretical contribution that smaller trials and those of lower quality produce more beneficial effects. So they take 2 larger samples of trials selected by process and criteria of their own choosing ("Sir, is that bias?")—the one of 110 from 200 or so trials available, the other 110 from a third of a million ("Sir? Is—" "Quiet boy!") These differing contexts of varying "borrowed strength" then yield samples of different characteristics, of most interest for this demonstration of the ravages of bias: Nineteen percent (19%) of one therapy (let's call it X) are of higher quality versus 8% of the other (let's say Y). Their teaching helps us predict that analysis of X will yield less beneficial effects than that of Y. This says nought about X or Y, just about trial biases. So, now for their crunch, will their theory work? Select down to 8 trials of X (from say 200) and 6 of Y (from say a third of a million) and they find that both work (i.e., an odds ratio of less than 1), but, X shows less treatment effect than Y. Bravo—the theory works! Oh, in passing, they happen to point out that X is homeopathy, so it cannot work, so it does not. And *The Lancet* anonymously announces the "End of Homoeopathy."[2] "Sir? Is that—" "Quiet boy!"

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