

Alternative Medicine: A “Mirror Image” for Scientific Reasoning in Conventional Medicine

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A reflection on the scientific behavior of adherents of conventional medicine toward one form of alternative medicine—homeopathy—teaches us that physicians do reject seemingly solid evidence because it is not compatible with theory. Further reflection, however, shows that physicians do the same within conventional medical science: Sometimes they discard a theory because of new facts, but at other times they cling to a theory despite the facts. This essay highlights the seeming contradiction and discusses whether it still permits the building of rational medical science. We propose that rational science is compatible with physicians’

behavior, provided that physicians acknowledge the subjective element in the evaluation of science, as exemplified in the crossword analogy by the philosopher Haack. This type of thinking fits very well with the Bayesian approach to decision making that has been advocated for decades in clinical medicine. It does not lead to complete and uncontrollable subjectivity because discernment between rivaling explanations is still possible through argument and counterargument.

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Discussions about the scientific value of alternative medicine quickly touch the raw nerve of conventional medical reasoning and medical wisdom. As such, alternative medicine is a useful “mirror” for conventional medicine (the idea that alternative medicine, in particular homeopathy, acts as a “forbidden mirror-image” for conventional medicine was described by Wiersma [1]): How one looks at the “other” may reveal more about oneself. Physicians’ response to the “other” may clarify neglected or hidden aspects of the scientific process in conventional medicine. This article examines aspects of the process of weighing scientific evidence in modern medicine. It is not primarily concerned with alternative medicine; rather, we reflect on scientific reasoning within medicine as a whole. Nevertheless, our train of thought in this article was triggered by examining our response to claims of scientific proof of the effectiveness of alternative medicine. We use homeopathy as the main example to discuss the scientific evaluation of alternative medicine because homeopathy has a long and extensive history of evaluation by randomized, controlled trials, and because the debate surrounding homeopathy makes the contradictions between seemingly solid evidence and scientific judgment most clearly visible.

HOMEOPATHY AND SCIENTIFIC EVIDENCE OF ITS EFFICACY

Homeopathy was devised in Germany by Samuel Hahnemann (1755–1843). It espouses the belief that whatever symptoms a substance causes in a healthy per-

son, a disease with a similar symptom configuration can be cured by small amounts of the same substance: *Similia similibus curentur* (“like cures like”), a principle that is already controversial in itself. Even more controversially, homeopathy claims that the more dilute a substance (if prepared by a series of shakings called “succussion”), the more “spiritual vital essence” is released and therefore the more potent the medicine that is created: Less becomes more (2). Remedies are often diluted up to or beyond Avogadro’s number (10^{23}), with a chance that not a single active molecule is left in the vial (2, 3).

Homeopathy has been debated for more than a century and a half. The debate has entered the modern medical era: Randomized trials have been performed and then summarized in meta-analyses. A recent meta-analysis (4), which built on previous ones (3, 5), found 89 trials that were described as adequate. The authors of the meta-analysis conclude that the data are “not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo” (4). The combined odds ratio showed a twofold benefit in favor of homeopathy, even after statistical correction for publication bias.

The future of homeopathy now seems bright: A meta-analysis of randomized trials concluded that homeopathic effects can no longer be seen as placebo effects and that the positive reported effects are not due to publication bias. Yet, most physicians working in conventional medicine vehemently dismiss this conclusion and find all kinds of counterarguments: The trials might

have been too small; there is only an overall effect, which might be due to the accumulation of several small biases (the position of one of us [6]); a repeatedly proven consistent effect has never been shown for a single indication with a particular regimen (7). In short, we want to find good reasons to discard the randomized trials.

Why? What is our ultimate reason for discarding the evidence from the meta-analysis of randomized trials on homeopathy? The authors of the meta-analysis showed that even the very best trials (as judged by the authors' methodologic standards) that used the highest dilutions (approaching or surpassing Avogadro's number) still showed a beneficial effect. That is materially impossible. The highest dilutions in homeopathic medicines are so high that it is not possible to determine by ordinary chemical principles which vial contains an “active product” and which one “placebo” (2, 3). Microbiologists know for sure that infinite dilutions of an antibiotic will never show any effect on bacterial growth. No physician will use an antihypertensive medication in a dilution that surpasses Avogadro's number. No oncologist would propose to dilute cytotoxic drugs beyond the limit of chemical detectability. Because of the impossibility of chemical effects, adherents of conventional medicine disbelieve the evidence from the randomized trials on homeopathy.

This leads to ever more intricate reanalyses of this meta-analysis. A novel proposition is to apply meta-regression analysis of measures of the quality of randomized trials (8). Through a meta-regression, one tries to estimate the effect of all individual quality elements that matter in particular trials (for example, size and blinding). This approach differs from that of the authors of the meta-analysis on homeopathy, who used an overall quality score. A new meta-regression analysis of the homeopathy trials found that “inadequate blinding” and “small sample size” strongly determined the overall positive effect of homeopathy (9). The two largest, adequately blinded trials on homeopathy showed no effect, a finding that is consistent with the intercept of the meta-regression that stood for “large blinded trials.” However, the authors are quick to point out that their results do not *prove* that the apparent benefits of homeopathy are due to bias. Nevertheless, those of us who think that the homeopathy results are impossible will see this meta-regression as a strong confirmation of our position.

DO TRIALS OVERTURN THEORY?

Once we recognize the tendency not to accept the evidence if it is incompatible with theory and to accept this reasoning as valid, we should analyze it: It might teach us a lot about how we actually reason in conventional medicine. When reflecting on our behavior in several controversies, we recognize that sometimes we accept the evidence from the randomized trial and overturn a theory—however beautiful it was—but that at other times we stick with the theory and dismiss the evidence.

Examples of both behaviors can be found in conventional medicine. One of the more fashionable and popular recent theories in immunology and infectious disease medicine concerned the immunologic mechanism of septic shock. Gram-negative septic shock was ascribed to circulating endotoxins produced by the bacteria; endotoxins would elicit a powerful cytokine response that harmed the organism itself. Animal research showed that gram-negative shock could be prevented if the blood was immediately cleared of circulating endotoxin and cytokines. This was done by using antibodies tailor-made by the stock-raising stars of the biotech industry. The first randomized trial, which studied antibodies against endotoxin, was reported as a success (10). However, doubts were expressed upon discovery that the positive findings concerned the subgroup of patients with gram-negative sepsis only. This discovery gave way to a lengthy discussion that is pertinent to our reflection on how we interpret “evidence.”

The problem was that at admission to an intensive care unit, the patient's infection cannot be identified as gram-negative or gram-positive (or as another type of infection), nor can one determine whether the infection led to bacteremia. Thus, in the trial, all patients with clinical suspicion of sepsis were randomly assigned. However, the type of infection was only known after 24 or 72 hours. The analysis was then restricted to patients with gram-negative bacteremia and clinical sepsis; these results showed a clear beneficial effect, supporting the immunologic theory and the animal experiments. Yet, the original report already indicated that the benefit almost disappeared when all randomly assigned patients were considered. The only logical conclusion was that the intervention had more untoward outcomes in the patients without gram-negative sepsis. Regardless of the

ensuing discussions (which also frowned on other subgroup analyses [11]), we can imagine that the investigators, as well as the journal's peer reviewers, originally found the restriction justified: Theory predicted that the intervention should work only in patients with gram-negative sepsis. Any untoward outcome in the remaining patients must have appeared to be a "freak accident." Subsequently, however, additional trials studied tailor-made antibodies against mediators of sepsis. Another picture emerged: no benefit, and sometimes even a small effect to the contrary (12).

Immunologists and infectious disease physicians recognized that the relationship among septic shock, endotoxins, and the cytokine response might have been more complex. It was not just a strong immunologic response to high levels of endotoxin that might be detrimental; the timing of the response might have an effect as well. An initial strong response to endotoxin might be beneficial, while an initial weak response might lead to dissemination of the infection. That dissemination, in turn, might lead to higher levels of endotoxin only at a later stage of the disease. Even some old animal experiments were seen in a new light (13, 14). Thus, in the end, the consistently negative findings of the randomized trials overturned the immunologic theory.

The inverse also happens. Recurrent vasovagal syncope is an annoying and sometimes dangerous condition. During the later phases of a syncope, profound bradycardia can develop. It is believed that this bradycardia might augment or prolong the symptoms. Therefore, some physicians have proposed the implantation of demand pacemakers to people with recurrent vasovagal syncope. Such pacemakers would not prevent the onset of syncope but might prevent its full development. A randomized trial of implantation of demand pacemakers had such positive results that the investigators stopped it prematurely (15). However, researchers who had studied the physiology of vasovagal syncope by using a tilt table to elicit syncope in healthy volunteers and patients had proven that syncope is due to vasodilatation and reductions in blood pressure and that cardiac pacing does not alleviate those symptoms (16).

This places us fully in the realm of the "homeopathy" dilemma: Physiologic theory, based on small-scale experiments, holds that pacing cannot work. Yet a randomized trial was overwhelmingly positive. The ensuing discussion (Wieling W. Personal communication) is

illuminating. Trial enthusiasts dismiss the physiologic studies as "small uncontrolled observations," while to physiologists these observations proved that pacing could not possibly work in any mechanistic sense. Consequently, the physiologically inclined physicians posed many a critical objection to the trial: Patients had not been selected because of profound bradycardia (on the contrary, tachycardia-producing isoprenaline was often used to elicit syncope during diagnosis, and only "relative bradycardia" was observed); the trial was open and unblinded (each cardiologist assessed his or her own patient by telephone); and during the average 1-week waiting time before implantation, no patient in the intervention group experienced syncope, whereas six in the placebo group did (suggesting a placebo effect or an overall randomization imbalance). In contrast, cardiologists point to the large effect of the pacemaker intervention, and they have electrophysiologic arguments of their own: New "dual pacing" would have a better influence on blood pressure than older "right-heart pacing" does. The discussion might go on for some time. It will certainly lead to new investigations, new randomized trials, and new electrophysiologic experiments.

EVIDENCE AND SPONSORSHIP

The example of homeopathy concerns a "class" of trials, while in the examples of conventional medicine we discussed specific instances and specific theories. However, some instances in conventional medicine also concern a "class" of trials. A recent review of hematology trials sponsored by the pharmaceutical industry found that most such trials had a positive result for the new product; this finding indicates that these trials could not have started under "equipoise," the genuine uncertainty that is necessary at the onset of a randomized trial (17). In contrast, publicly funded trials favored the investigated drug half of the time, as expected under equipoise. The authors of the review discuss many reasons for this difference, including the possibility that the designing of sponsored trials may lead to conditions favoring the success of the new product.

Another outstanding example is that of sponsored randomized trials on nonsteroid anti-inflammatory drugs (NSAIDs). A review of such trials found that all sponsored studies favored the new product (most of the time because of superior efficacy or lesser toxicity) or found the new product to be at least as good as the

competitor product (18, 19). This review reported that the competitor product was often administered in rather low dosages. Because many of the newer and older NSAIDs resemble each other pharmacologically, the finding that sponsored trials of NSAIDs give predominantly positive results for the sponsor's product is, a priori, as impossible as the predominantly positive results of trials on homeopathy. Therefore, we suspect that the same mechanisms are at play: a departure from “equipoise” due to the accumulation of larger or smaller biases in design, analysis, or reporting.

THE CROSSWORD ANALOGY

Our overall conclusion from the preceding examples and others, alternative and conventional (20), is that in conventional medicine we sometimes accept the randomized trial evidence and discard the theory but at other times we stick to the theory and dismiss the “facts.”

What is the basis of such reasoning, and can it be justified? The U.S. philosopher of science, Susan Haack, tries to steer a middle course between “naive” hypothetical-deductive dogmatism (that is, one immediately discards a theory upon experimental falsification, which in reality never happens), and a postmodern “anything goes” approach (that is, truth is just another commodity that we negotiate about, a matter of societal convention and silent pacts, that is completely dependent on time, place, and person). How can we on the one hand acknowledge that a scientific experiment might be set up in a spirit of “conjecture and refutation” yet believe that its interpretation might be colored by theoretical preconceptions? Haack proposed the “crossword analogy.” In her words (21):

The clues [of the crossword] are the analogue of experiential evidence, already-completed entries the analogue of background information. How reasonable an entry in a crossword is depends upon how well it is supported by the clue and any other already intersecting entries; how reasonable, independently of the entry in question, those other entries are; and how much of the crossword has been completed. An empirical proposition is more or less warranted depending on how well it is supported by experiential evidence and background beliefs; how secure the relevant background beliefs are, independently of the proposition in question; and how much of the relevant evidence the evidence

includes. How well evidence supports a proposition depends on how much the addition of the proposition in question improves its explanatory integration. There is such a thing as supportive-but-less-than-conclusive evidence, even if there is no formalizable inductive logic.

Thus, when the randomized trials on antiendotoxin repeatedly did not fit with the previous entry about the theory of septic shock, that previous entry was removed. Inversely, we do not want to remove the notion that “infinite dilutions cannot possibly work.” While the former reaction might seem reasonable to most observers, why is the latter acceptable? Can we dismiss “evidence” because it does not fit with an already existing theory?

A BAYESIAN OUTLOOK

As a matter of fact, physicians are pretty well used to discarding “facts” because of theory. This is called the Bayesian outlook in diagnostic thinking. When confronted with a middle-aged woman who has vague chest symptoms and a host of psychosocial problems, the physician might still order electrocardiography, just for certainty. However, if the echocardiogram shows a slight ST-segment elevation, the physician will shrug his shoulders and mention it as an aside in his report. His reasoning is that many persons have ST-segment elevations without consequence and that the patient's symptoms do not fit with a truly cardiac abnormality. However, if the same electrocardiogram belongs to an elderly man with a history of typical angina, the physician will exclaim, “Ha! You can see it on the cardiogram.” The same fact gets a different meaning according to diagnostic suspicion.

This Bayesian outlook has been formalized in medical decision making, but it has also been shown to apply to the interpretation of clinical trial evidence (22, 23). Results of randomized trials can be seen as results from the “statistical lab” that come in just like electrocardiogram results come in. Depending on our prior belief, we will accept them or not. If our prior belief is strong, as with, for example, homeopathy, we will shrug our shoulders when confronted with randomized trial evidence: There are so many reasons why trials can turn out positive. Inversely, when we still believed in the original endotoxin-septic shock paradigm, we believed the results from the first randomized trials. And when

we are confronted with positive results from industry-sponsored trials, our a priori suspicion about a lack of "equipoise" will make us dismiss such trials more easily.

One of the great theoreticians of epidemiology, Jerome Cornfield (the inventor of both the odds ratio and logistic regression), who had a firm Bayesian outlook in his statistical thinking, recognized the problem when he wrote about the problems of interpreting the results from randomized trials: "good scientific practice . . . places the emphasis on reasonable scientific judgment and the accumulation of evidence and not on dogmatic insistence of the unique validity of a certain procedure" (24).

This quote looks like a foreshadowing of Haack's crossword analogy. Cornfield's idea was initiated by his reflection on the status of randomization in study design, and therefore also has bearing on debates on the relative merit of randomized and nonrandomized evidence (25–27).

ARGUMENTS AND COUNTERARGUMENTS

This brings us to the status of arguments about evidence: What arguments count? In a personal communication, Gerard de Vries, professor of the philosophy of science in Amsterdam, the Netherlands, taught one of us about the "U.S.–Japanese electron argument." It runs as follows: A physics experiment is carried out in Japan, and the same experiment is carried out in the United States. Suppose that the outcomes differ. One of the investigators might then propose, "Well, perhaps electrons in the United States and in Japan are different." Most people with some knowledge about science will tend to dismiss this argument immediately and will suspect that something went wrong in one of the experiments. This reaction would occur because most people expect that explanations on the atomic level are the same, wherever on earth. However, the investigator might remain stubborn and maintain that people who stick to such a position are no longer true scientists: They dismiss the very experiments showing that Japanese and U.S. electrons are different!

The answer is that the position of that investigator is "too easy": It is too easy to bend the theory to the experiment each time that one sees a reason to do so. If we leave the position that explanations on the atomic scale should be the same on all places on earth, we leave

meaningful physics; from that moment onward, anything goes. Therefore, we prefer to take a second look at the Japanese and U.S. experiments. We want to determine whether they differed in their execution in a way that might explain the different results. The same goes for homeopathy and infinite dilutions. Accepting that infinite dilutions work would subvert more than conventional medicine; it wrecks a whole edifice of chemistry and physics. That price is too high: Too much knowledge that really works in our day-to-day world is built on existing chemistry and physics. We do not want to discard this because of a few randomized trials. Therefore, we prefer to take a hard look at this type of "evidence."

While the discussions about alternative medicine do highlight the nature of our reasoning and put its strengths and weaknesses under a stark spotlight, we should not forget that we do continuously apply these rules—without knowing it—when discussing the merits of a new therapy or a new theory in conventional medicine.

SCIENCE VS. BELIEF

Our position is a difficult one: Highlighting the judgmental nature of our theoretical positions inevitably leads to the suspicion that we cannot "prove" these positions, that some positions might ultimately be amenable to change, and that other persons have an equal right to cling to their positions.

Of course, in principle, all positions are amenable to change. It remains possible that out of the blue, from the observation of a single patient, from local folklore, or even from alternative medicine, some principle that is of value emerges. After all, that is how medicine started with "willow bark" and "foxglove"; we ended with salicylates and digitalis.

Nevertheless, science is not just another belief system that can be replaced by any other belief at will. Science is a construct of arguments and counterarguments that we try to fit together in a mental crossword puzzle. Certain propositions are simply not acceptable because they are just unproven flights of imagination. For example, in discussions about epidemiologic case-control studies, one can always dream up potential bias and confounding, but that does not mean that they exist. Other arguments might be valuable in themselves

but can be dismissed; arguments about potential bias and confounding in epidemiologic studies can often be verified by stratification or replication.

To further scientific arguments and counterarguments, we continuously produce new experiments and new observations—and have new rounds of discussion around them, to examine how they fit. In day-to-day science, we see this most clearly in the midst of a controversy still lacking sufficient evidence—that is, when the crossword is far from completed and large blank areas surround the few entries. Decisions about the next correct entry, and about how to obtain the next entry, will retain a subjective element. When a theory is still developing, different scientists will cling to different opinions, and that is legitimate. However, all strive to a common end point, according the word of Sir Dominic Corrigan, Irish physician and statesman (1802–1880), one who never ran away from a controversy: “Whether my observations and opinions be disproved or supported, I shall be equally satisfied. Truth is the prize aimed for; and, in the contest, there is at least this consolation, that all the competitors may share equally the good attained” (28).

An important proof for the value of this process is that science “works,” from its ancient forms in the construction of temples or cathedrals to telecommunication and experimental gene therapy. In an illuminating essay on the “science wars,” Stephen Gould accepts that science is socially constructed and that it is therefore uncertain whether humanity should by necessity have arrived at its present state of knowledge (29). If science had taken another detour, part of our scientific world might be different, but it would always reflect a reality “out there.” In his own words: “The true, insightful and fundamental statement that science, as a quintessentially human activity, must reflect a surrounding social context, does not imply either that no accessible external reality exists, or that science, as a socially embedded and constructed institution, cannot achieve progressively more adequate understanding of nature’s facts and mechanisms” (29).

THE MIRROR

Our purpose in this article was to show that the confrontation concerning the results of randomized trials in alternative medicine teaches us a lot about our way

of reasoning in conventional medicine. The extreme challenge presented by alternative medicine is that some trials have positive findings when that is impossible; this situation leads us to reflect that the same happens in conventional medicine. We surmise that the same mechanisms that lead to positive trials in alternative medicine may lead to false-positive trials in conventional medicine. In conventional medicine, however, this is much more difficult to see because we tend to believe in the pathophysiologic mechanisms that are proposed to explain the trial results. Where strong prior beliefs operate (for example, in alternative medicine trials or in industry-sponsored trials), we will want to maximize guarantees that scientific research has been done properly. For example, we should be especially careful to determine whether equipoise was guaranteed in the design of a trial and whether all results of all trials have been reported (17). The realization of the difficulties that confront medical research in this area will stimulate the development of new tools to identify which randomized trials are credible and which ones are not. Nevertheless, in the ultimate judgment, reasoning—and thus subjectivity—will remain unescapable.

We should be grateful for debates about alternative medicine: They open our eyes to the nature of our reasoning in conventional medicine. We should forever keep an open mind, but, according to the late Petr Skrabanek, not so open that our brain falls out (30).

Note added in proof: A recent randomized trial of dual pacemaking in patients with syncope selected participants according to cardiac response on tilt-table testing (31). The benefit of pacemaking was as high as seen in the previous study discussed above (15). After pacemaker implantation, however, susceptibility to elicited tilt-table syncope (the entry criterion) was unaltered. This finding will lead to continued debate between physicians who predominantly stress pathophysiologic reasoning and those who adhere to trial results.

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