

Theory Based Medicine and the Role of Evidence: Why the Emperor Needs New Clothes, Again

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Version of 4 March 2009

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Abstract

The evidence based medicine movement (“EBM”) was established to combat capricious reasoning in clinical care, particularly arguments from authority. Critique of authority and appraisal of evidence remain EBM's core values, and should be revisited in this current era of EBM's maturity and considerable influence. At this stage, we encounter a new form of under-questioned authority: evidence from well-designed and methodologically appraised RCTs. RCT evidence is now prized even on some occasions when it is incapable of providing meaningful information – in particular, when underlying causal theory is inscrutable. This is the case with many health interventions whose mechanisms remain “black boxes” without compelling explanations. A review of recent clinical trials of remote intercessory prayer illustrates this problem. The findings of these trials are uninterpretable and inapplicable, due to unresolved and fundamental theoretical problems with their hypotheses and premises. Yet, this trial evidence has gained remarkable scientific credibility and high profile dissemination, largely on the warrant of rigorous RCT methodology. The case of remote intercessory prayer evidence helps to identify some systematic blind spots in the institutions of EBM. As EBM has long counseled, clinicians and policy makers should indeed be skeptical of causal arguments in the absence of empirical evidence. However, empirical evidence in the absence of good causal argument is likewise occasion for skepticism. Medicine – even evidence-based medicine - is theory-based at its core. EBM must cultivate greater capacity to address the crucial role of theory, in both the generation and the use of experimental evidence.

Acknowledgements

I am grateful to Jeremiah Hurley, Geoffrey Norman, Deborah Cook, Nuala Kenny, Andrea Smith and the editors for their very helpful comments and suggestions on earlier versions of this manuscript. Lydia Garland, Deirdre DeJean, and Dorina Kirilova provided much appreciated research assistance. This project was supported in part by CIHR operating grant # MOP – 79427. This work also benefited from the resources and collegial environment of the Centre for Health Economics and Policy Analysis, which is funded in part by the Ontario Ministry of Health and Long Term Care. Responsibility for the content of this paper and its conclusions remains my own, and should not be attributed to any of those thanked here.

“The principal chapters of the second part...are also founded upon attested facts and observations, without suffering the illusions of theory to influence and pervert the judgment.”

- James Lind, 1753, p. xii

“There is nothing so practical as a good theory.”

- Kurt Lewin (widely quoted)

“It is a common weekday opinion of the world that praying people are not practical.”

-Sir Francis Galton, 1883, p. 277

Introduction

The evidence based medicine movement (hereafter, “EBM”) was established to combat capricious reasoning in clinical care – in particular, arguments from authority based on intuition, experience, or pathophysiologic theory. Theory, in particular, has been characterized as something opposed to evidence - and an inferior source of knowledge (Guyatt et al. 2000). In EBM’s formative years,

“EBM advocates proclaimed a new paradigm and seemingly pitted EBM against the traditional knowledge foundation of medicine, in which the key elements are understanding of basic mechanisms of disease coupled with clinical experience. The latter is epitomized by the individual authority (“expert”), or, better still, collective medical authority...” (Haynes 2002)p. 2)

Critique of authority is indeed one of EBM’s core values. The movement has replaced much dogma- or status-based authority with more science-based authority. EBM’s proudest and most teachable moments are when it can show that the “Emperor had no clothes” - that randomized

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controlled trial (“RCT”) or meta-analysis evidence has corrected conventionally authoritative beliefs. Other exemplars include historical occasions when an RCT supported a therapy whose pathophysiologic rationale became clear only much later, as basic science caught up with clinical science (e.g, James Lind’s trial of citrus to prevent scurvy in 1747).

EBM’s leaders successfully popularized the idea that clinical decisions should be supported by evidence, and that the well designed RCT provides the most credible evidence of therapeutic effectiveness (Guyatt et al. 2000; Devereaux and Yusuf 2003). Lower status is given to observational studies of effectiveness, and little to non-empirical scholarship. Favoritism for RCTs has softened as EBM’s leaders suggest that observational and qualitative research, as well as expertise and experience, can usefully augment experimental evidence (Haynes 2002). Nevertheless, an RCT-idealizing value system has become deeply rooted in medicine, in some ways beyond the intentions of its more thoughtful leaders. A similar “evidence-based decision-making” ethos now flourishes in the administrative and policy sectors of the health system.

Concurrent with the rise of EBM, causal ideas about health and disease have expanded well beyond biology and physiology to concern social, economic, and psychological phenomena. Interdisciplinary and lay knowledge posit additional variables and dynamics in health. Complex health care and health system interventions arise from these myriad beliefs. To cut through the tangle of causal claims and arguments, and to ascertain simply “what works” for clinical practice, health system researchers now promote the RCT as the design of choice for evaluating complex health programs and policies (Oliver et al. 2008). Complementary and alternative medicine (by definition, involving treatments that lack conventional biomedical explanation) also increasingly turns to RCTs to support interventions’ clinical or scientific legitimacy. The medical RCT was established as a method for testing biomedical interventions, which are explained (or at least in principle explainable) by the natural sciences. However, over time it has become used to address interventions whose mechanisms are comparative “black boxes”, based on myriad social science, natural science, and lay belief systems. We increasingly subject to RCTs complicated interventions we understand vaguely, or cannot explain at all.

The RCT’s many years as EBM’s “gold standard” methodology leaves a legacy of sophisticated techniques for designing and critiquing clinical trials, but essentially none for critiquing the rigour of trial hypotheses and theoretical assumptions (Ashcroft 2004). Equanimity about whether an intervention works prior to its test (equipoise) has lapsed into tolerating

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uncertainty about the reasons an intervention should work at all. In this era of EBM's maturity and considerable influence, one form of authority - expert opinion - has been replaced in many minds with another - evidence from well-designed RCTs.

The RCT has inadvertently become the new “Emperor with no clothes.” Attired in sophisticated methods, RCT evidence is sometimes welcomed as authoritative even when it is incapable of providing meaningful information – particularly, when the underlying causal theory is inscrutable. Is it legitimate to experiment in humans with interventions whose hypothesized effects are unexplainable? Are trials of “black box” interventions as methodologically sound as trials of causally explained interventions? Is it worthwhile to test a complex and unexplained intervention, if only to demonstrate it is ineffective?

The answer to all of these questions is “no”. RCT evidence without grounding in adequate causal theory provides information of little scientific value. Coherent and plausible causal explanations are necessary for evaluating experimental hypotheses, conducting trials, treating human subjects ethically, interpreting findings, and applying results to future studies or decisions. The rigour of experimental procedure has little bearing on this scientific problem; rigour of theoretical reasoning is crucial. This paper will review the growing medical research program in remote intercessory prayer (hereafter, “remote prayer”) to illustrate the nature of this problem in the context of EBM, and to suggest lessons for health research.

Theory and causation

Theory, like evidence, is a broad concept with many meanings. The *Oxford English Dictionary* lists two definitions useful for understanding the relationship of theory to scientific evidence and practices. The first is as a system of knowledge:

“4. a. A scheme or system of ideas or statements held as an explanation or account of a group of facts or phenomena; a hypothesis that has been confirmed or established by observation or experiment, and is propounded or accepted as accounting for the known facts; a statement of what are held to be the general laws, principles, or causes of something known or observed.”(Oxford English Dictionary 1989)

This describes the type of theory used and pursued by science. Theory systematically binds new information of all kinds (ideas, data, etc.) into coherent knowledge. A knowledge of general

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laws, principles and causes (how things are generally *supposed* to work) is necessary to generate the hypotheses and methods of any experiment, as well as to interpret experimental observations and findings. Another definition casts theory as a knowledge base for practice:

“4. b. That department of an art or technical subject which consists in the knowledge or statement of the facts on which it depends, or of its principles or methods, as distinguished from the *practice* of it.”(Oxford English Dictionary 1989)

Theory mediates between evidence and practice. It guides the adaptation of study interventions to real, nonexperimental situations. There are several levels of theory in empirical health research. Ontology lies at the base and dictates what sorts of entities may exist and therefore be sought (e.g., matter? meaning? causal laws? deities?). Epistemology, at the next layer, suggests how these presumed entities might become known (e.g., observation? interpretation? inductive or deductive logic? contemplation?). From these foundational premises rise broad belief systems, within which any given fields' research questions can be specified and answers methodically sought. Philosophers of science have variously characterized these broad belief systems that organize and delimit scientific inquiry, and give findings their meaning. The most familiar is Thomas Kuhn's "paradigm"; alternative formulations include Kuhn's "disciplinary matrix," Lakatos' "research programme", Laudan's "research tradition," or Fleck's "thought style." Common to all is the idea that scientists produce and convey new insights only in the context of a widely shared (if imperfect and evolving) belief system about the essential nature of the phenomena they study. On this prevailing consensus rest the descriptions and explanations of phenomena that constitute the variables, hypotheses and models of causal experimentation.

The ferment of new knowledge -- where new ideas are generated, tested, and flourish or decay -- occurs at the surface of a vast ocean of tacit assumptions about the nature of things. Some health disciplines work within entirely different bodies of theory (e.g., physiology vs. cultural anthropology): the knowledge in one could be neither generated nor supported by the assumptions of another. This poses intractable problems for some forms of interdisciplinary collaboration. Operational scientific theories need not be entirely correct-- indeed, a hallmark of scientific progress is the continual revision and refinement of theory. But to be useful, prevailing theory must be coherent and intelligible within its field. Some fields entail no coherent body of assumptions on which to develop and sustain enduring new scientific knowledge. Causal models cannot make sense if they rest on a belief system that is irrelevant, incoherent, or altogether missing. At the frontiers of any field, researchers face the challenge of keeping their

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empirical questions afloat on supporting belief systems, and developing theory that will support
new questions.

Clinical trials of remote intercessory prayer

Clinical trial research of the clinical effectiveness of remote intercessory prayer illustrates how generation and use of evidence depend upon underlying theory. “Remote intercessory prayer” refers to people praying to God for the healing of others, without the others’ knowledge, and with no interaction between those praying and those prayed for. This type of prayer has now been subjected to RCTs as a health intervention, and the findings disseminated as evidence to inform clinicians. Scholars outside the empirical program have criticized the trials’ problematic ideological and theoretical premises, and trial findings remain scientific and clinically uninterpretable. Even so, researchers within the empirical program call for further RCTs. This paradox reveals important scientific blind spots in experimentally oriented clinical research.

In the 19th century, Francis Galton demonstrated that royalty tend to die younger than commoners, despite being so much more widely prayed for (Galton 1883). Serious medical trials of remote prayer began sporadically in the 1960s, with two small negative trials – one double blinded of 48 patients with rheumatic or psychological disorders (Joyce and Welldon 1965) and one triple blinded of 18 childhood leukemia patients (Collipp 1969). By the 2000s, remote prayer research joined mainstream medical research. Prestigious funding agencies (e.g., the U.S. National Institutes of Health), institutions (e.g., the Cochrane Collaboration, Harvard University, Duke University, the Mayo Clinic), and journals (e.g., *Lancet*, *Archives of Internal Medicine*, *American Heart Journal*, *Science*) have served as vehicles for reports of remote prayer research. In the U.S., at least \$4.7 million has been spent on remote prayer RCTs, nearly half by federally-funded agencies (Carey 2006). Eighteen apparently authentic trials can now be identified (Byrd 1988; Collipp 1969; Joyce and Welldon 1965; Walker et al. 1997; Sicher et al. 1998; Matthews, Marlowe, and MacNutt 2000; Krucoff et al. 2001; Tloczynski and Fritzschi 2002; O’Laoire 1997; Matthews, Conti, and Sireci 2001; Harris et al. 1999; Aviles et al. 2001; Krucoff et al. 2005; Mathai and Bourne 2004; Palmer, Katerndahl, and Morgan-Kidd 2004; Seskevitch et al. 2004; Benson et al. 2006; Astin 2000). Together, these trials involved 6,099 human subjects, 19% of whom were not informed that they were participating in a trial of remote prayer as a health intervention.

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Few RCTs find associations between remote prayer and outcomes (variously defined as intermediate clinical endpoints, self reported health status, morbidity, or mortality). In a trial of 393 CCU patients, Byrd found a statistically significant positive effect of Christian prayer “to a Judeo-Christian God” on 6 of 26 outcome variables, and on a global hospital course score (Byrd 1988). Results were highly profiled by the news media, including the front page of the *New York Times* in 2004 (Carey 2004) and again in 2006 (Carey 2006). Harris et al were unable to replicate Byrd’s findings, and found no effect on additional 31 additional clinical variables (Harris et al. 1999). However, they developed a CCU course score expressly for their study, for which they found a statistically significant 10% improvement in the treatment group. These two studies are frequently cited as positive evidence of the effectiveness of remote prayer. A small trial of mixed religious and secular “distant healing” for AIDS patients found decreased hospital use, lower incidence and severity of new illnesses, and improved mood (Sicher et al. 1998). Two more obscure trials concerning pathological mental states also show positive results (O’Laoire 1997; Tloczynski and Fritzsich 2002). The early trials that showed statistically non-significant effects (e.g., (Joyce and Welldon 1965; Collipp 1969)) are sometimes also cited as positive evidence by later investigators.

Some positive trials of remote prayer have been disingenuous. A highly publicized study concerning *in vitro* fertilization (Cha, Wirth, and Lobo 2001) is now believed fraudulent (Harris 2004; Flamm 2005). A study of retroactive remote intercessory prayer (intercession on behalf of people whose outcomes occurred long before the prayers) appeared in a light-hearted Christmas issue of *BMJ* (Leibovici 2001). The nonsensical “trial” was correctly done, yet it was published not as scientific evidence regarding prayer, but rather as a cautionary demonstration that a large enough RCT could support a theoretically implausible intervention (Leibovici 2002). However, Leibovici’s provocative demonstration is not consistently recognized for what it is. Others have cited the trial as evidence in favour of remote prayer effectiveness (Palmer, Katerndahl, and Morgan-Kidd 2004), or objected to Leibovici’s failure to get informed consent (Turner 2006). The hypothesis of retroactive effect is discussed as a serious possibility in the reports of other trials (Tloczynski and Fritzsich 2002; O’Laoire 1997). Leibovici’s study is the largest in a 2007 Cochrane review of prayer (Roberts, Ahmed, and Hall 2007), included without caveat about its very unusual premise.

Most trials are negative. One finds increased complications in coronary artery bypass graft recipients who were certain (and correct) that they were prayed for (Benson et al. 2006). An inconclusive Cochrane review was first conducted in 1997, and updated in 2005 and 2007.

The most recent reviews 10 studies (including the controversial Cha and Leibovici studies) involving 7,807 participants. The review concludes in summary that, “Most of the studies show no real differences” (Roberts, Ahmed, and Hall 2007) p. 2), and that,

“It is not sensible to interpret any of the interesting results with great confidence... Most data are equivocal. The evidence presented so far is interesting enough to justify further study into the human aspects of the effects of prayer. However it is impossible to prove or disprove in trials any supposed benefit that derives from God’s response to prayer.” (Roberts, Ahmed, and Hall 2007) p. 1)

In an appendix, the review recommends key design features for a future study of remote prayer. Such a trial should be conducted “anywhere,” would involve 300 adults with any “physical or mental health problem,” and would subject the treatment group to an intervention of, “personal, focused, committed and organized intercessory prayer on behalf of another,” for a minimum of 26 weeks (Roberts, Ahmed, and Hall 2007) p. 21). Most negative RCTs of prayer similarly conclude that the hypothesis remains promising, and recommend further study with modified trials. A systematic review concludes, “...we are aware of the epistemological limits of even the best designed experimental investigations. But we believe that many questions in the area of prayer and health will ultimately be best addressed through the use of experimental methods” (Masters 2005)p. 337). The authors suggest that further work focus on definition and operationalization of key variables and control conditions, especially for background prayer.

The Theoretical Basis of Remote Intercessory Prayer Interventions

Why are most remote prayer trials negative? What do the positive findings mean? What would a dramatically positive trial mean? Will future studies, with modifications of control, setting, participants, or prayer practices, contribute new knowledge? Would a future systematic review ever declare this body of research to be definitive? Can the evidence be used by either scientists or clinicians, and how? Answering these questions requires an examination of the theoretical premises of the remote prayer research program. Crucial are ontological assumptions about the causal nature of the phenomena under study.

There are two theoretical belief systems for understanding remote prayer RCT questions and answers. These will be referred to simplistically as the “God” belief and the “Force” belief, and introduced briefly in lay terms. The God belief is based on religious metaphysics. At the

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behest of the intercessor, an omniscient, omnipotent, supernatural being (“God”) intervenes at will in the world. Most religions assume that God governs the world according to divine purposes that humans can only partly apprehend, and that God responds to prayer within the context of God’s own imperatives. God’s beneficence is normally presumed, as is God’s displeasure at sin (which in Judeo-Christian traditions may include testing God or inauthentic prayer). Most religions have norms regarding the appropriate disposition of persons who pray, as well as the appropriate content and occasions for prayers. God is aware of all human needs and desires, even in the absence of prayer. Intercessory prayer is offered in relationship with God. This relationship influences the very things prayed for, as well as the meaning of any apparent consequences of prayer. Most religions recognize the importance of healing, compassion, or transcendence to overcome suffering, but beyond this, specific health states have unclear valence given the God belief. Faith might reframe infirmity and death as necessary within the larger context of God’s plan. Prayers to a God would be heard and answered in a manner different from a granted wish or a sufficient or necessary cause of effect: when prayer works, one gets whatever God wants one to have, and not necessarily the thing asked for. Importantly, any law governing God-mediated prayer would not be a natural scientific law, but a theological one. An answered prayer is a singular event, each time occurring at the pleasure of God. Instrumentally effective prayer therefore would not be replicable. Nor should it rely systematically on the skillfulness of intercessors, or the demographics or diagnoses of those prayed for.

The Force belief is potentially more compatible with conventional scientific knowledge. On this understanding, prayer generates a physical force that passes directly from the intercessor to the patient without an intervening deity. However, this Force is not yet specified. The fact that other invisible but powerful physical forces, such as electricity or electromagnetic radiation, can play a role in health and illness perhaps supports the ontological expectation that other, yet-undiscovered forces could be at work in the world. Such ontological hunches render remote prayer amenable to experimental testing, in principle. However, the appropriate trial design and apparatus would depend on more specific (but lacking) theories about what constitutes the Force and how it works. Presumably, the Force must be generated by thoughts or words, must be transmitted physically to the patient, and must reach the physiological receptors where it is translated into the specific effects requested (or the nonspecific effects such as “healing” or “wellbeing”). Four Force explanations have been suggested (Leder 2005), although none are explicitly employed in any of the prayer RCTs: (1) an unknown energy signal, (2) a warp of space-time, (3) quantum non-local entanglement, and, (4) the collapse of “a probabilistic wave

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function into a single outcome”. Interfaces between mind, prayers, and Forces remain mysterious, as are possible mechanisms by which a religiously-minded thinker (as compared to other minds with other thoughts) might generate the Force. Some of these Force explanations depart from established physics by locating the forces at a human scale (e.g., space-time warps usually being attributed to massive celestial objects, and quantum behaviour to subatomic nuclei). Electromagnetic forces fall dramatically with increasing distances, which would problematize the “remoteness” of prayer. While the Force idea does not prescribe any value system concerning health outcomes, neither does it conflict with the conventions of health research that consider disease and disability to be bad outcomes, and death catastrophic.

This rudimentary description of the God and Force belief systems highlights three theoretical problems that undermine remote prayer RCT evidence: (1) the essentially nonscientific nature of causal theories consistent with the God idea, (2) the lack of specific and plausible forces articulated under the Force idea, and (3) the uninterpretability of trials that conflate assumptions from these two fundamentally incompatible belief systems.

The first theoretical problem is the incompatibility of the God belief with RCT methods. If individual souls and relationships with God matter, samples of patients (and intercessors) comprise unique individuals rather than represent populations. Generalizability beyond the study participants is impossible for every trial, regardless of selection criteria. Some characteristics (religious affiliation or fervor, for example) might affect intercessors’ or patients’ favour with God, but with uncertain effect. The content of the intervention is determined not only by the intercessors’ prayer practices, but also by a supernatural, willful intelligence, so replicable, mechanistic action cannot be expected. If God is omniscient, it is not clear what intercessors would need to know about the people for whom they pray. If God is omnipotent, it would be impossible to shield members of a control group from God’s care; neither would high, low, or background “dosages” of prayer necessarily alter its effect in predictable ways (Sulmasy 2006). Good outcomes would be defined tautologically, by a positive spiritual interpretation given to whatever occurs, including death. In short, the God belief offers no operational framework on which to build falsifiable predictions or interpretable experimental designs. It renders all outcomes open to many interpretations, none of which can indicate whether the intervention “worked” in a clinical sense.

The Force belief, however, should support features typical of an RCT design: population sampling, randomization to control and treatment groups, attention to background treatment

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levels, the appropriate configuration and intensity of the study intervention, dose-response relationships, hypothesis testing, and the attribution of significant positive outcomes to the effectiveness of the intervention. The Force idea is less deeply ontologically problematic than the God idea. Yet it remains too underdeveloped to operationalize key phenomena and guide experimental design. For example, should remote prayer work if vast distance separates the intercessor from patient? Possibly, on quantum mechanical assumptions (setting aside the concern that people might not behave like subatomic particles), but probably not, on electromagnetic energy signal assumptions. In the absence of a theory of how worded thoughts (prayer) could be translated into forces by the mind, it is not clear how much information intercessors would require to deliver their Force to the right patient and problem, or what obstacles might interfere. One study required intercessors to know the patient's "first name, date of birth, diagnosis of end stage renal disease, favorite color, favorite food, main hobbies or interests" (Matthews, Conti, and Sireci 2001), another used anonymous identifier codes only (Mathai and Bourne 2004). A theory is needed to understand patients' ability to receive the remotely dispatched Force. For example, some suggest it matters whether the patient's disease is life-threatening (Roberts, Ahmed, and Hall 2007), without explaining why. If prayer directs some Force, it is conceivable that prayer variants might also misdirect, disperse, or change it, and render it ineffective or harmful. This has implications for informed consent, as well as clinical science. Designing the procedures for a remote prayer RCT requires a specific theory of causal mechanism, beyond the presumption that a force of some sort may be at work.

A third theoretical problem in the remote prayer research program is the conflation in trial procedures of God ideas with ontologically incompatible Force ideas. On close examination of methods, no remote prayer trial seems to adhere exclusively to either God or Force beliefs. Trials tend to implicate the God idea when, despite the expectation of powerful physiological effects on serious health conditions, they waive patients' informed consent to the intervention (Harris et al. 1999; Palmer, Katerndahl, and Morgan-Kidd 2004), employ exclusively religious intercessors (Harris et al. 1999; Aviles et al. 2001; Matthews, Conti, and Sireci 2001; Seskevitch et al. 2004), or use only religiously conventional prayers (Seskevitch et al. 2004; Krucoff et al. 2001; Krucoff et al. 2005). For example, Harris et al (Harris et al. 1999) employed Christian intercessors who attended church weekly and prayed daily, and required them to (voluntarily) agree with the statement: "I believe in God. I believe that He is personal and is concerned with individual lives. I further believe that He is responsive to prayers for healing made on behalf of the sick." (Harris et al. 1999) p. 2274) No two trials examined the same manifestation of prayer, and in several trials investigators could not describe the content or procedure of the prayers

their intercessors used as the study interventions. More than one trial required one group of intercessors to pray for patients, while a second group prayed for the prayers of the first intercessors (Krucoff et al. 2005; Cha, Wirth, and Lobo 2001), expecting this to achieve a higher dose of prayer. It is not intuitive how this might be so, in the absence of divine intervention. The God idea is implied in concluding suggestions that future studies address patients or intercessors of varying religious beliefs or spiritual maturity (Matthews, Conti, and Sireci 2001; Masters and Spielmans 2007). Studies that address diverse prayer interventions or health conditions, as if these represent a single phenomenon, tend to imply that specific physical and biological pathways do not matter. This is also more consistent with the omniscient, omnipotent God explanation.

Despite God belief assumptions, many of these same investigators also entertain the Force idea when they raise concerns about the interference of background prayer (Harris et al. 1999; Aviles et al. 2001), or other dose-response issues (Aviles et al. 2001; Krucoff et al. 2005). Force beliefs support the study of prayer as a part of a class of interventions that include nonreligious remote or alternative healing maneuvers (Seskevitch et al. 2004; Krucoff et al. 2005). Non-God beliefs are implicit in analyses of study demographics and speculations about generalizability (presumably God would not discriminate on such terms). Populations in remote prayer studies have been characterized for example as the Southeastern U.S. “Bible Belt,” “well educated, white” members of local churches (Palmer, Katerndahl, and Morgan-Kidd 2004), or “ethnic minorities of lower socioeconomic status” (Matthews, Conti, and Sireci 2001). Some suggest future studies address more diverse populations (Aviles et al. 2001) or diseases (Matthews, Conti, and Sireci 2001).

Observers of the remote prayer research program find it difficult to discern the underlying belief systems from such inconsistent methodological choices. Turner suggests RCT investigators must subscribe to the Force belief, because its assumptions are the only ones that support experimental methodology (but notes that intercessors cannot possibly share the investigators’ Force orientation if they are to practice authentic prayer)(Turner 2006). Masters opines to the contrary that remote prayer studies *de facto* subscribe to the God belief when they exclusively employ religious intercessors and religious prayers (Masters 2005). The review of methodologies here suggests that remote prayer researchers fail to commit to either belief system. The investigators themselves avoid making ontological or causal claims. Typically, they explicitly deny the God explanation, but without articulating an alternative Force explanation. Most studies state that the investigators have no preconceived ideas about what may be at

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work. The Harris et al study (which required churchgoing Christian intercessors to profess their explicit faith in God) for example disclaimed that: "...we have not proven that God answers prayer or that God even exists. It was intercessory prayer, not the existence of God, that was tested here" (Harris et al. 1999). A study of prayer by two Christian ministers for a largely Christian patient sample (Matthews, Conti, and Sireci 2001) concludes, "...the specific mechanism of effect for these findings could not be conclusively determined. Intercessory prayer is a complex, multifaceted intervention, similar to cognitive-behavioral therapy and other psychological programs..." (Matthews, Conti, and Sireci 2001)p.1184). Others explain their negative findings: "It should be noted that, in part due to the study's many limitations, this study did not measure the 'power of God,' nor should prayer offered for patients by loved ones, relatives, and friends be interpreted not to play a potentially important role in the healing process..." (Aviles et al. 2001)p. 1198).

Remote prayer researchers' reluctance to articulate any theory of how the prayer intervention is supposed to work extends to the 2007 Cochrane review (Roberts, Ahmed, and Hall 2007), which summarized trial evidence for patients, clinicians, managers and policy makers. The authors acknowledge the incompatibility of the God theory with RCT methods. They also cite Old and New Testament Biblical passages and verses suggesting that God may not cooperate with blinded controlled study designs, or may value specific outcomes differently than researchers do:

"Some people of faith might argue that any such trials are putting God to the test and are against biblical commands (Deuteronomy 6:16). However we do not feel this is the case. For those who believe in a loving God this is an attempt to apprehend or uncover something of His creative process. There remain great questions for people of any or no faith regarding illness and prayer, not least why a loving God would heal some but not others." (Roberts, Ahmed, and Hall 2007) p. 13)

The report asserts that findings have nothing to do with God, yet no alternative theory is offered, beyond euphemistic suggestions that there might be "an effect of prayer not dependent on divine intervention" (Roberts, Ahmed, and Hall 2007)p. 2) or that the trials may "...show some other effect that may be the result of things other than the action of a God..." (Roberts, Ahmed, and Hall 2007)p. 13).

While remote prayer investigators have shied from the matter of causation, the media has pointedly addressed it. The 2004 *New York Times* cover story for example noted the U.S.

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federal government's substantial financial investment in this research program, and investigated its ideological foundations and practice implications. The story correctly identified the RCTs' inconsistencies with both God and Force beliefs. A quoted theologian describes the studies as "...promot[ing] an infantile theology that God is out there ready to miraculously defy the laws of nature in answer to a prayer;" a scientist argues that, by definition, the research questions are not scientific, therefore "a total waste of time and money" (Carey 2004). A senior advisor at the National Center for Complementary and Alternative Medicine (in the U.S. NIH) asserts that mechanisms need not be understood for an intervention to be tested, citing pharmaceutical analogies. On the matter of practice and policy implications, he points out that, of the 45% of U.S. adults who pray for health, "...many of them were poor people with limited access to care. 'It is a public health imperative to understand if this prayer offers them any benefit.'" (Carey 2006)p. A1)

Faced with uninterpretable findings, most remote prayer investigators hesitate to draw actionable conclusions from their studies, but almost all suggest more research is needed. A Mayo Clinic RCT of 799 CCU patients, addressing its negative results, suggests: "These results do not suggest a contraindication to prayer, and further study is warranted to define the role of IP [intercessory prayer] on quantitative and qualitative outcomes and to identify end points that best measure the efficacy of prayer in a variety of patient populations." (Aviles et al. 2001) p.1198) The Cochrane Collaboration review echoes trial investigators' calls for further trials with modified designs. Few studies address the theoretical challenges in their discussion of future work to be done. One uncharacteristically critical closing statement reads: "The potential influence of multiple factors operating within an *unknown theoretical framework* renders a significant challenge toward future investigations of the efficacy of intercessory prayer" (Palmer, Katerndahl, and Morgan-Kidd 2004)p. 447, emphasis mine). A largely negative meta-analysis characterizes the trials as essentially "atheoretical," and concludes that,

"Though atheoretical individual findings linking prayer and particular measures of health can be important, greater research yield and subsequent practical relevance is likely to come from studies that are housed within an integrated nexus of theoretical ideas and empirical data. A starting point is for investigators to provide greater clarity and specification of explicitly hypothesized relationships between independent and dependent variables" (Masters and Spielmans 2007)pp. 35-36).

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Despite hints at definitional and operational problems, no investigator identifies the depth of ontological confusion on which the research question rests. By contrast, scholars from outside the trial program – physicians, ethicists, theologians, psychologists, journalists – have identified many of problematic assumptions (Halperin 2001; Bishop and Stenger 2004; Masters 2005; Sulmasy 2006; Turner 2006; Masters and Spielmans 2007). As non-empirical scholarship, however, this highly relevant work was systematically excluded from the 2007 Cochrane review and not cited in the background discussion. Neither are the theoretical works referenced in the RCT reports, with one exception (Halperin 2001) cited by 3 trials (Mathai and Bourne 2004; Benson et al. 2006; Palmer, Katerndahl, and Morgan-Kidd 2004).

Theory based medicine

Medicine – even evidence-based medicine - is theory-based. Theory gives data their status as facts, guides the search for new facts, and lends findings their meaning and implications. Medicine relies on theory to develop interventions, test them, generalize findings to new situations, and apply research findings to individual cases. Theories about “what causes what” rest on more fundamental theories about how things “must work,” and what the “things” themselves must be. On these fundamental commitments we can build the coherent belief systems that define disciplines, fields, or research programs by specifying the general types and range of causal variables and dynamics possibly at work.

For much of medicine based on traditional natural sciences (“biomedicine”), specific causal theories are well grounded. The established underlying belief systems (e.g., represented by the disciplines of biology, chemistry, physiology, etc.) and their ontological bases are no longer considered problematic. For example, if researchers do not know quite how a particular drug works, they still have a good idea of how to find out empirically, and where to look. They also have the scientific means to describe exactly of what the tested intervention (the drug) consists. The biomedical beliefs underlying most clinical trials (e.g., of pharmaceuticals) do not beg the wholesale investigation of theoretical premises.

However, some health interventions depart from the scientific belief systems of biomedicine. Some of these may belong to other disciplines with their own coherent belief systems, on which meaningful causal hypotheses and research questions can be built, and informative RCTs can be designed. Other interventions, however, lack coherent theoretical

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justification at the deeper level of a disciplinary belief system, or yet deeper ontology. Science has places for nurturing creative and iconoclastic ideas, but by the time these are translated into interventions and hypotheses for human trials, causal theories should be clear, rigorous, and amenable to critique. Without the requisite theoretical groundwork, researchers cannot rigorously operationalize variables, determine proper experimental conditions, or attribute observations to phenomena.

It is not exemplary science, and is bad ethics, to test a “black box” intervention whose causal relationship to health and harm cannot be fathomed. To be evaluated scientifically, the rationale behind an intervention must be transparent (Ashcroft 2004). Experimental evidence about unexplainable interventions may not only be pragmatically worthless, but even misleading or harmful. EBM’s current focus on improving experimentation and knowledge dissemination methods neglects the parallel need to develop capacity for identifying and addressing foundational problems with causal theories. Nowhere is this blind spot more evident than in the case of remote prayer research, where investigators confess they do not know what might be going on, whether their methods addressed key factors, or how best to interpret their own findings – yet all agree more RCTs are needed.

Is experimentation with a-theoretical “black box” interventions a serious problem, with ramifications beyond the peculiar research program on remote prayer? The remote prayer research program is an instructive example for three reasons: (1) it maps some institutionalized blind spots in EBM’s current capacity to evaluate evidence, (2) it provides a cautionary tale of the (in)consequences of testing what we cannot explain, an idea popular with some EBM-oriented researchers; and, (3) it is one of a growing class of health interventions with complex, interdisciplinary rationales that will face similar challenges of experimental and causal justification.

First, the remote prayer research program offers a good test case to see how far a theoretically unpremiered research question can go in the academic industry that generates, publishes, and disseminates medical evidence. The answer is all the way: from small, fringe projects to large, federally funded trials in leading academic medical centres, and beyond this, through medicine’s most prestigious journals to dissemination by the Cochrane Collaboration and the front page of national newspapers. All along the way, the research findings remained uninterpretable and without consequence as scientific or practical knowledge. The oversights that allow such work to pass are systematic and institutionalized in contemporary EBM. We are

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overcredulous when faced with large samples and sophisticated trial and analysis procedures, sensing (mistakenly) that these are more scientifically demanding than theoretically articulate study questions. Pressed by clinicians and policy makers to figure out “what works” to meet health needs, we often treat matters of “how” things work as an intellectual detour to be taken on occasions of leisure or curiosity, or by other sorts of scientists. Resolute to ignore opinion, we sometimes mistakenly dismiss causal reasoning as another form of bias or as a failure of equipoise. When training new researchers, we do not systematically cultivate skills for discerning a rigorous causal argument, or for appraising its underlying assumptions (causal models, belief systems, ontologies and epistemologies). When reviewing trial reports, we tolerate vague, euphemistic articulation of causal ideas, especially if outside our native disciplines. In the medical literature, we segregate theoretical scholarship from empirical research. Theoretical inquiry often appears informally in editorials, letters, or special commentaries; rigorous and extensive analyses are most likely to appear in separate, less empirical journals.

Second, the argument that we need not entirely understand remote prayer to test it echoes a common argument made about other health interventions. Some leaders in the evidence based decision making movement argue that a solid explanatory theory is not imperative for RCTs of complex interventions in cases of widespread use, urgency, or even a limited underlying “state of knowledge” *per se* (Medical Research Council 2000). However, complex interventions are rarely replicated outside research settings; they are adapted. Without theoretical grounding, RCTs will leave users wondering which aspects of the study intervention were crucial to its success and which irrelevant - and whether adaptations could be effective, useless, or harmful. When RCT findings fail expectations, either the theoretical assumptions behind the methods are unsound, or the evidence is true – but which? Evidence alone cannot guide this choice. This dilemma (the “Duhem-Quine problem”) arises in all research, because methodology is always imperfect and causal hypotheses underdetermined to some degree. To deem any evidence definitive, then, is to make a theoretical resolution. Trialists who claim RCT evidence does not require an understanding of mechanism sometimes cite James Lind’s classic 18th century controlled trial of citrus for scurvy. Interestingly, historical accounts suggest that Lind did employ an explicit, if mistaken, causal theory to guide his choice of interventions to test. He had hoped his experiment would enlighten theoretical debates about effective treatment of scurvy. Unresolved causal theory affected the trial’s impact on practices, because effectiveness of citrus was incorrectly attributed to acidity (rather than ascorbic acid). For years, interventions based on Lind’s trial involved inexpensive (and unfortunately vitamin C-free) acidic diet

Theory Based Medicine and the Role of Evidence: Why the Emperor Needs New Clothes, Again supplements. The slow “research uptake,” as we might call the problem today, has been attributed to the resistance of arrogant authorities to good experimental evidence (Harvie 2002). However, some historians blame the delay on Lind’s neglect of theoretical issues implied by his experiment, and the consequent inability of others to make sense and use of his findings (MacBride 1991).

The third reason remote prayer offers an instructive case study is that remote prayer is by no means the only mysterious “black box” intervention being evaluated with RCTs and systematic reviews. Within a flourishing evidence-based decision making ethos, policy makers and clinicians are now trained to respond to new interventions with a demand to see an RCT (or preferably, many RCTs) of effectiveness. RCTs are being applied to more non-biomedical interventions, programs, and policies (e.g., low-income family financial benefits to improve child health (Lucas et al. 2008)). Health care interventions themselves are changing, as rationales depart from the conventional natural science belief systems of biomedicine. Complex, and particularly interdisciplinary interventions imply numerous causal variables interacting in a tangle of multidirectional dynamics. Unless enough of these variables are identified and accounted for in experimental designs, such interventions remain for practical purposes black boxes, with unknown working parts and an undetermined range of possible beneficial and harmful effects. In situations of interdisciplinary collaboration, experts find themselves in uncomfortable novice roles, and shy uncharacteristically from asking foundational questions (Giacomini 2004). Pellegrino has highlighted this as an ethical problem placing special onus on researchers to clarify the meaning of their studies: “...the greater the gap in expertise between the purveyor of the evidence and her or his audiences, the greater the complexity of the evidence itself, and the more general or serious the policy implication, the greater culpability. We are all vulnerable to misinterpretation of evidence once we are outside the field of our own expertise.” (Pellegrino 1999), p. 39)

The EBM movement has perhaps too successfully inspired the values of “evidence above all, and RCT above all evidence.” Now is a good time to return to EBM’s primary values of questioning authority and building scientifically rigorous bases for practice. As EBM has long counseled, clinicians and policy makers should indeed be skeptical of causal arguments in the absence of empirical evidence. However, empirical evidence in the absence of good causal argument should likewise occasion skepticism. EBM must become less cavalier about this latter problem, and less squeamish about acknowledging the inevitable role of theory in the generation and use of evidence. Because of the Duhem-Quine problem and related issues, the

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boilerplate statement that “more research is needed” is a possible conclusion for any trial. It is a scientifically meaningful conclusion only when residual questions are specified, and the full spectrum of inferential designs and methods (understood as a network, not a hierarchy (Bluhm 2005)) are considered for fitting approaches (Norman 1999). In some cases, lingering doubts are best addressed through theoretical inquiry or the hard scholarly work of developing a rigorous and informative research question (Norman and Eva 2008). Until we become more adept at identifying, diagnosing, and correcting theoretical problems in health research, “black box” experiments will waste scientific resources, exploit human participants, and generate inscrutable findings. Evidence-oriented policy makers, clinicians, and peer reviewers should resist undue allegiance to large, logistically impressive experimental trials. Evidence festooned with complex methodological procedures, and even brandishing the gold standard of the RCT, remains naked without its “foundations” of credible theoretical assumptions. Our Emperor needs new clothes, again.

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