

Evidence-based medicine: The epistemology that isn't

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Little attests to the weakness of the clinical academic terrain like the way in which it allows its own intellectual culture to be subjugated to that emanating from lesser disciplines: economics, social studies (I can't bring myself to use the word science), or accountancy. There have been two such fashions in the recent medical past—audit and, more recently still, the growth of evidence-based medicine (EBM). Both share much in common: little sympathy or understanding of natural science, but rather look to operational research or accountancy for solutions; a shady relation with coercion, by the state or others; and the boast, with strident echoes of Orwell ringing just over the horizon, of replacing culture with platitudes—*EBM good, clinical judgment bad*—how edifying.

I want to argue that even by its own limited standards EBM fails. In particular, it fails because it excludes many forms of reliable knowledge. Second, the importance of the randomized clinical trial (RCT), that which EBM places at its intellectual heart, has been overgeneralized and overstated. Third, I also want to raise the question of why EBM so suddenly has become attractive to a significant number of clinical researchers.

First the name. It is of course not just tiresome, but also mischievous. Would anybody wish to boast about practicing medicine not based on evidence? This name, however, seeks an exclusivity for a particular church of belief, particularly that based on RCTs. Opponents are somehow ridiculed by the sophistry of confusing reliable knowledge with that produced from a RCT. A rhetorical device perhaps, but a pernicious one. A moment's reflection on the therapeutic revolution that characterized the middle of this century shows that advance came from a catholic collection of strategies for advancing knowledge, including case-studies, $n = 1$ experimental

studies, and often the sheer weight of efficacy in unblinded series of patients receiving novel treatments.¹⁻⁵ To travel back even further, would we now claim that the discoveries of Pasteur, Koch, and Ehrlich (or even Hebra's rediscovery of the role of the *Sarcoptes* mite in scabies) do not represent reliable knowledge? No, of course not. Ever since the school of logical positivism tried this abortive intellectual adventure over one century ago—and failed—we know that there is no formula, no finite state calculus, no explicit ratiocination that allows the obtaining or weighting of absolute knowledge. Discovery still owes more to imagination than checklist. Would we really set about grading Darwin or Mendel on a scale of 1 to 4 for reliability? Oh, and while we are at it, what about a meta-analysis of quantum electrodynamics?

The problems of the RCT

So how does the randomized controlled trial fit into the panoply of research strategies in medicine? Austin Bradford Hill, by many considered the father of the RCT, was clear on this issue although his words appear sadly neglected by many who would claim intellectual kinship: "If one came to the conclusion that the only way to find out the truth about a medication was to use a controlled trial, it would not mean the pendulum had swung too far but that it had come completely off its hook."⁶ (p. 108) The RCT is a powerful generic technology for estimating the effects of interventions. Its strength lies in the attempt to remove bias due to differences in allocation between groups. But what it does not do, and where much confusion resides, is remove judgment from a discussion of efficacy or, even wider off the mark, dictate clinical usage. The limitations of the RCT are many: when should you do a study with a new treatment, after people are already using the treatment or before; how much heterogeneity is there in subgroup response; are the trials done in populations that match those in the clinic; what do you make of studies that give contradictory results; are the end points clinically relevant; and what exactly does a summary value mean for individual people? Although the list is long and old, what has become

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increasingly common has been the attempt to use the RCT to produce spurious measures of efficacy with treatments of modest effect, hidden behind summary values, and with decisions expropriated from the clinical context. (I will say nothing of the attempts to use such flawed reasoning, whether by government or private corporations, to deny patients treatment). Since the patients in your clinic did not take part in the original studies, extrapolation to them is simply that, an extrapolation, an additional hypothesis if you like. But a trial can only predict the effect of a future intervention as a function of its intellectual coherence—and this has nothing to do with statistical confidence or *P* values. These limitations are only exacerbated by the sad pursuit of smaller and smaller treatment effect values. Simply put, treatments with large benefits may fall into practice quickly, whereas those showing only modest effect will continue to be rehashed in meta-analysis after meta-analysis, Cochrane review after Cochrane review. Efficacy, of course, may end dissent, although not always, “Eppur si muove.”

EBM: Why now?

None of the above arguments are novel or new.^{7,8} The limitations of the RCT have been textbook fodder for half a century and the delusion of averaging all the data as a way of describing the universe much older still. A more interesting question is surely why has the EBM creed suddenly become popular? What, for instance, is the relation between “basic” science and EBM? Must we relinquish pathophysiological reasoning for summary measures of black-box pragmatic studies? Vandenbroucke has written persuasively and with great insight on these issues.⁹⁻¹¹ However, I will approach the issue from a more dermatological angle: How should we use phototherapy?

How should we use phototherapy?

If you were to collect a heterogeneous group of patients with inflamed skin and test some new modality of phototherapy in an RCT, how useful would this be? The answer clearly is, not very. Without a theoretical underpinning of nosology and, in all likelihood, pathophysiology, it would be impossible to translate these results to other individuals. Treating disease in this black-box way would mean that we learned little from the study to guide us to advance therapy for the next study. Without any pathophysiological reasoning we would not, for instance, know whether we should use phototherapy twice a day, twice a week, or twice a month. Now doesn't this sound familiar! So, how do we make progress? One solution is of course to imagine an endless series of RCTs, but it is immediately clear

that we will quickly have more permutations than we will ever be able to practically afford. Therefore it is not possible to run away from theory as to how the therapy is working and what entities are being treated. Once the RCT becomes a mere technical exercise, a test of a mere “null hypothesis” rather than a test of a scientific theory, its value is diminished simply because we can't test an endless series of arbitrary designs. Of course, I would also argue that there is an aesthetic dimension to consider: many black-box studies are dull, wasteful of energy and youth, and surely belong outside institutions of learning.

So do we just wait for more “hot off the bench” results from the molecular biology lab to tell us what to do?

Now, one temptation at this stage is to imagine that somehow we can build our clinical practice from the bottom up. And the example of phototherapy remains informative in this context. How informative is cell biology in terms of guiding optimal treatment strategies? Does all that high-profile laboratory-based research into DNA repair, apoptosis, SOS responses allow us to predict how to use phototherapy? How will we factor in the genetics of skin type, family history, history of burning, and so on? In truth, the answer must be: very little. And perhaps herein lies one reason for the alacrity with which EBM has been championed: a disenchantment or perhaps alienation with the clinical utility of many model systems (*sic*). And this leads naturally to the question of whether we really just expect too much too soon from our heroic reductionist program.

The record of jumping intellectually from Eppendorf (test tube) to patient is a poor one, with many 180-degree turns on the way.^{4,5,12-14} I would argue that this isn't a failing of biology per se, or reductionism as an approach, but merely that we are not yet at a stage where we are able to produce quantitative and predictive models designed on cell biology experiments to explain whole organ functioning and the behavior of whole populations. Akin to the realization in neuroscience that you must study problems at a number of levels, from the molecule through system neuroscience to behavior, there is a danger that our picture of biomedicine has become fractured, polarized into either the minutiae of intracellular signaling on the one hand and on the other, large ecologic studies with little resemblance to natural science. Clinical science of course lies somewhere in between.^{4,5,15,16} Indeed, the real heuristic value of EBM may be as a landmark to sail from rather than to.

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