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SPECIAL ISSUE

'*One mission accomplished, more important ones remain*': commentary on Every-Palmer, S., Howick, J. (2015) How evidence-based medicine is failing due to biased trials and selective publication. *Journal of Evaluation in Clinical Practice*, xx, yyyy

Peter Wyer MD[1] and Suzana Alves da Silva, MD, PhD[2]

[1]Associate Professor of Medicine, Columbia University Medical Center, NYC, NY
[2]Senior Researcher, Amil Assistencia Medica Internacional and National Institute of Cardiology, Rio de Janeiro, Brazil

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Correspondence
Dr Peter Wyer
Department of Medicine
Columbia University
446 Pelhamdale Avenue, Pelham
NY 10803
USA
E-mail: pwyer@att.net

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Abstract

Every-Palmer and Howick suggest that evidence-based medicine (EBM) is failing in its mission because of contamination of research by manufacturer and researcher-motivated bias and self-interest. They fail to define that mission and to distinguish between the EBM movement and the research enterprise it was developed to critique. An educational movement, EBM accomplished its mission to simplify and package clinical epidemiological concepts in a form accessible to clinical learners. Its wide adoption within educational circles fostered critical literacy among several generations of practitioners. Illumination of bias, subterfuge and incomplete reporting of research has been a strength of EBM. Increased uptake and use of clinical research within the health care system properly defines the failing mission that eludes Every-Palmer and Howick. Responsibility for failure to make progress towards its achievement is shared by virtually all relevant streams within the system, including policy, clinical guideline development, educational movements and the development of approaches to evidence synthesis. Discordance between the epistemological premises pervading today's research and health care community and the complex social processes that ultimately determine research use constitutes an important factor that must be addressed as part of a remedy. Enhanced emphasis on and demonstration of alternative approaches to research such as realism and realist synthesis and the momentum towards development of a learning health care system hold promise as guideposts for the rapidly evolving health care environment.

Between the idea
And the reality
Between the motion
And the act
Falls the Shadow
(T.S. Eliot, The Hollow Men)

Criticisms of evidence-based medicine (EBM) began to appear shortly after publication of a hallmark concept piece in the *Journal of the American Medical Association* in 1992 [1] and reflected a variety of perspectives ranging from the epistemological [2,3] to the purely practical [4,5]. Defenders of EBM were quick to point out that many of these reflected misconceptions of what they were advocating and seeking [4,5]. We previously identified the continuation of this pattern in connection with a book authored by strong EBM adversaries [6]. Specifically, the book in question persistently confused EBM with the clinical research enterprise and wandered between different contexts of application of research evidence to health care policy and practice. The article by Every-Palmer and Howick (E-P/H) in this issue of the *Journal of Evaluation in Clinical Practice* propagates recurrent points of confusion, that is, equation of EBM with the clinical research enterprise and wandering context of application. One of the authors of the article in question, Howick, has published a defence of fundamental precepts of EBM, including the originally proposed hierarchy of knowledge posited in the original 1992 article, which placed trial evidence at the top of a pyramid in which pathophysiological knowledge and clinical skills were 'de-emphasized' [7]. Howick's defence is

something that even many committed EBM advocates might currently be hard pressed to endorse. Indeed, after the initial wave of criticism [2], proponents of EBM offered a well-known fallback position that appeared to soften the epidemiological hard line of the original announcement. The new model placed consideration of clinical circumstances and patient values and preferences on an equal plane with trial evidence [8]. Summarizing, we have strong adversaries [9] and strong advocates [7] of EBM reflecting fundamental confusion with respect to what it is that they are opposing or advocating for. This suggests that something more than suboptimal scholarship, incontrovertibly present in these examples, is at play in generating this confusion. We will explore this in some depth as this commentary unfolds.

The article by E-P/H is uninformed. It presents a thesis that, unscrambled, might be summarized as the danger of corruption of EBM through the effects of industry manipulation of research design and reporting, including suppression of results that fail to corroborate clinical superiority of the product at hand. In the course of developing their thesis, the authors systematically fail to acknowledge and cite the multitude of published reports and analyses on the part of EBM founders and protagonists that have brought these very subterfuges to the light of day. Over the years, many aspects of design that serve to further non-scientific objectives of the trialists have been prominently exposed by EBM founders and advocates [10]. These include the manipulation of composite endpoints in which common but clinically trivial outcomes are given equal weight as those that are less frequent but carry high impact such as death [11], the practice of stopping trials prior to meeting the original target enrolments when early results transiently show a benefit [12], and emphasis upon relative as opposed to absolute measures of effect [13–16]. Furthermore, reporting bias, that is, selective publication of trial outcomes, patient data or of entire trials, has been emphasized in the EBM literature since the beginning of the movement [14–16].

Inattentive review of cited literature is reflected in the article by E-P/H. They identify two publications as evidence of EBM success [17,18]. In fact, both citations report the failure of the health care system to provide care supported by trial evidence to more than 50% of eligible patients, a finding that would later be generalized by McGlynn *et al*. [19] in a widely cited landmark study which indicted the US health care system for failure to consistently deliver evidence-based care to the patient population. A large portion of E-P/H's article is devoted to the impact of publication bias in distorting reports of efficacy of antidepressants. However, they fail to mention the 2010 revelations regarding the antidepressant drug roboxetine [20,21]. This episode received prominent coverage in the popular press after a systematic review published in the *British Medical Journal* [20] revealed that the original trial reports had excluded 70% of the patient data and that adding this data to a meta-analysis resulted in disappearance of an originally reported benefit. To be sure, E-P/H address issues of general efficacy of antidepressants and antipsychotics as a class, rather than the merits of any particularly drug within that class. Nonetheless, it is hard to fathom why they would not have mentioned roboxetine in this context had they been aware of it. In summary, E-P/H's manuscript reflects failure to adequately research topics being addressed and misinterpretation of articles being cited.

The mission of EBM

Lapses in scholarly thoroughness are not what makes the article by E-P/H worthy of a commentary. Let us return to the issue of what EBM is and consider what criteria would properly define its success or failure. E-P/H, Howick in the previously cited book [7], and the authors of Tarnished Gold [9], all adopt or refer to the same definition of EBM, coined by Sackett *et al*. [22]:

> Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients [22].

In his 2011 book, Howick posits the following excerpt from the original 1992 *Journal of the American Medical Association* article [1] as a 'definition' of EBM:

> Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiological rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research [7].

This, of course, is merely a statement of attributes of EBM. Howick eventually settles on Sackett's definition. Uniformly missed by E-P/H is that none of the statements of what EBM 'is' or 'does' define an actionable mission. No mission statement was included in the original 1992 article nor in subsequent publications of the sponsoring 'EBM Working Group', and indeed, E-P/H, whose article centres on the assertion that EBM is failing in its mission, also fail to identify one.

So was there an unstated mission of EBM at the point it was announced as an educational initiative in 1992? A cynical view might be that the unstated mission was to foster an ascendance of clinical epidemiology over the basic sciences and clinical tutelage within academic medicine. Certainly, the circumstances and context within which the initiative was born were consistent with that. Indeed, it was the basic science departments at the mother institution, McMaster Health Sciences Center in Ontario Canada, which rebelled against it even more than the clinical departments. However, a more generous imputation can be recognized not only within the 1992 article, but also and most importantly from the training and dissemination process that led to and followed it. The practical, or 'operational', educational mission of the effort that gave birth to EBM was to develop independent and critical thinking and literacy among doctors in training with respect to clinical research. This was best known to the clinical educators and learners who came to McMaster during the 1980s and 1990s to take part in the annual workshops. As told in the preface of the second edition of the Users' Guides compendium [23], during the previous decade, David Sackett had inaugurated an educational series in the *Canadian Medical Association Journal* for doctors and doctors in training called 'Readers' Guides to the Medical Literature' [24]. The series presented structured criteria for detecting design-related flaws in published research reports. During the following decade, Sackett led the annual workshop series at McMaster at which clinical educators learned to use the Readers' Guides approach to critiquing journal articles. The emphasis was on identifying flaws in published research reports. Indeed, the standard 'boiler plate' of the Readers' Guides scheme uniformly culminated in the suggestion 'go on to the next article', when all criteria for excellence failed to be met. With the advent of EBM, which coincided with Gordon Guyatt's assuming the position of residency programme director for internal medicine at McMaster, the emphasis in the

workshop, also now headed by Guyatt [25], moved away from merely 'tearing articles to shreds', in favour of a more constructive attitude of deriving useful information from published reports, even in the presence of flaws. Nonetheless, the emphasis continued to be critical appraisal. To this day, the teaching packages used at the workshops are made up of article reprints conforming to specific study designs, combined with worksheets revolving around criteria for evaluation of the likelihood of bias, the importance and precision of results and, to a lesser extent, issues of applicability to practice.

EBM, as an educational movement, was anti-authoritarian. What drew clinical educators and learners from North America to the McMaster workshops, and to similar events internationally [25], was the prospect of empowering clinicians with enhanced research literacy. In so doing, these experiences encouraged participants to resist bowing blindly and automatically to professorial authority, be it asserted from the standpoint of pathophysiological reasoning or of personal clinical experience. Workshop attendees and participants had little interest in the ideology of the EBM movement such as expressed in the 1992 article. Nor were they inclined to use research to supercede clinical reasoning and decision making. The dissemination of EBM during the 1990s and early 2000s was carried by these experiences in a fashion not reflected in the literature that fostered the debate. Enhancement of independent judgment and decision making among clinicians through increased research literacy, albeit largely confined to the domain of assessment of risk of bias, was particularly appealing within primary care and related specialties, such as general internal medicine, family medicine [26] and emergency medicine [27].

In summary, EBM, an educational initiative, used instructional journal series' and a three decade long workshop series to foster research literacy [28] and critical appraisal skills among clinical learners. From the standpoint of the article by E-P/H, there is a remarkable irony here. Although lacking a published mission statement, the thrust of EBM was exactly the contrary of fostering uncritical adoption or rejection of the results of clinical research. Furthermore, as already noted, the movement produced the most poignant exposés of industry and researcher-motivated subterfuge ever published [10].

EBM as a generalized packaging label

Once introduced, the term 'evidence-based medicine' enjoyed explosive uptake throughout the health care environment [29]. It became associated with levels of policy, health care management and implementation that had little to no connection with the content of the 1992 *Journal of the American Medical Association* article and subsequent journal series. The term 'evidence-based guidelines' had already been introduced by David Eddy [29,30]. Writing in *Health Affairs* in 2005, Eddy bemoaned the fact that 'EBM', as a trademark, was being taught almost exclusively as a discipline pertaining to individual patient care and decision making and that guidelines were being ignored.

As a call for integrated educational initiatives, we believe that Eddy was on the mark. However, confusion regarding the nature, relevance and appropriate usage of the term 'EBM' abounds across the various sectors of health care. As an example, the 2011 Institute of Medicine (IOM) report, which calls for upgraded standards for clinical practice guidelines [31], largely confines its discussion of relevant clinical epidemiological background to the 'EBM' literature pertaining to individual patient care. It barely mentions the work of Eddy or the other precedents for systematic consideration of clinical trial data in the course of guideline development. Perhaps compounding potential confusion, leading members of the original EBM Working Group who co-authored the 1992 *Journal of the American Medical Association* article and the Users' Guides series subsequently became members of an international collaboration aimed at developing strict epidemiological criteria for clinical guideline development. 'Grading Recommendations Assessment, Development and Evaluation (GRADE)' [32] presents a quantitative system for scoring the quality of evidence from controlled trials and observational studies in connection with clinical guideline development and seeks to develop a common nomenclature for communicating strength of evidence and recommendations in such contexts. The GRADE system shares a common body of epidemiological and methodological concepts with EBM. However, it emerged from a different process from that spawned the educational movement. Still, further complexity is added to the landscape by virtue of the fact that the GRADE collaboration invites crossover between recommendations intended for the guidance of practitioners and patients in clinical decision making and those aimed at the development of health care policies on the part of insurers and regulators [33]. The National Institute for Health and Clinical Excellence (NICE), whose recommendations are used to guide coverage policy within the UK National Health System, adopted the GRADE system in 2007 [34].

The research-health care interface

Given the above, it is perhaps understandable that a superficial survey of relevant literature may encourage loose usage of the label EBM to refer to now one and now another aspect of the research-health care interface. Given the controversy triggered by EBM, both when introduced and since [28], undifferentiated use of the term only serves to mystify the topic of discussion. Conversely, given the anti-historical misuse of the term, an attack on 'EBM' easily translates to an assault on the scientific foundations of health care itself. It would seem that a properly differentiated and consistent framework for understanding that interface is in order. Figure 1 presents four historically distinct but interrelated streams. On the left, we have the developments leading to the concept of evidence-based clinical guidelines. The original report of the Canadian Task Force on the Periodic Health Examination [35] is commonly credited with having first introduced consideration of clinical research as a routine aspect of developing such recommendations. The relevance of clinical research to health policy and resource planning was importantly spurred by the work of Wennberg and colleagues at Dartmouth [36]. They showed large variations in practice within small geographic areas in New England that could not be explained by differences in population demographics. The Cochrane Collaboration, which has served as the pace setter for compiling information from clinical trials into systematic reviews since 1993 [37], was inspired by the writings of British epidemiologist, Archie Cochrane. Cochrane called for systematic collection and compilation of all prior and future clinical trials in a way that would allow their easy access to the health care system [38]. Finally, the trajectory on the right hand side of Fig. 1

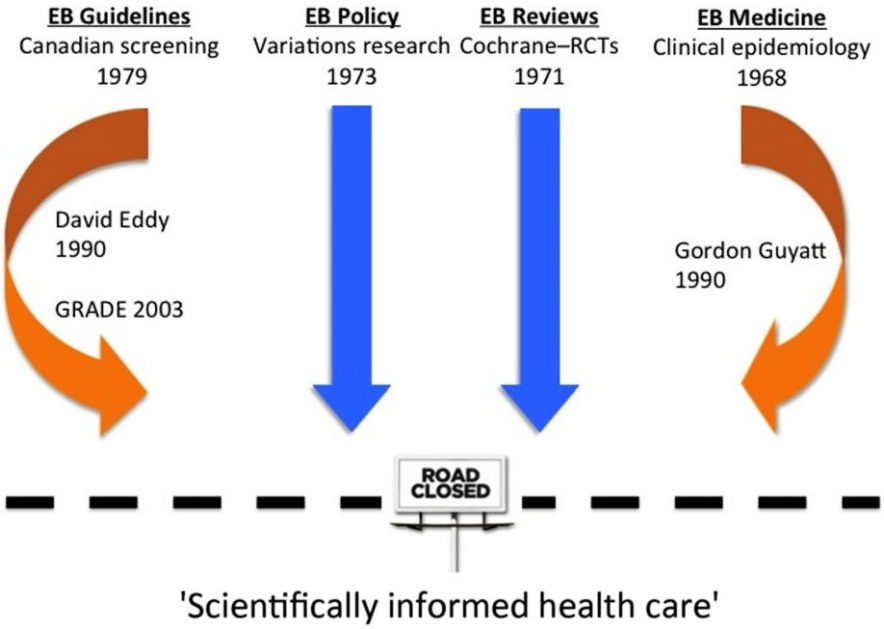

Figure 1 Illustrating four independent streams of development pertaining to the use of research in the health care system. The term 'evidence-based' (EB) was independently introduced by different individuals working in different streams. The bottom of the figure is intended to illustrate the barriers responsible for the widely perceived underutilization of research within the system. The shift from 'evidence-based' to 'scientifically informed' may embody an important clue to how these barriers may be overcome.

reflects the development of clinical epidemiology [39], a discipline that led directly to 'EBM', the 1992 educational initiative, and also nourished the development of all of the other parallel streams. Specifically, leaders of clinical epidemiology, Sackett, Feinstein [40], Fletcher [41] and others, developed criteria that influenced reporting standards for randomized trials [42] and systematic reviews [43] and also contributed to protocols used in clinical guidelines frameworks such as GRADE [44].

It is historically important to recognize that the four streams in Fig. 1 originated and developed independently over the course of four decades. They traverse the interface of clinical research with health policy, clinical guidance, education of practitioners and their interactions with patients and their health problems and the process of deriving estimates of clinical effects from the results of a multiplicity of trials. Rejecting the use of a single term to refer to the fruits of historically independent initiatives is important from several standpoints. Firstly, it avoids attributing credit to a small number of individuals for developments that involved hundreds of talented innovators. Secondly, it prevents a muddling together of elements of a complex process into an undifferentiated mass impervious to analytical inquiry. Thirdly, adherence to a differentiated view makes it less likely that over generalized constructs such as 'success or failure' of an erroneously labelled enterprise can lead to misdirected conclusions. Fourthly, and perhaps most importantly, it allows recognition that a much broader packaging label is appropriate. We suggest that the true and timely subject is the interface between clinical research and the entire health care system. To the extent that conflict-of-interest generated bias is corrupting, it is certainly the quality of healthcare that is corrupted, not, as suggested by E-P/H, the movement that has done the most to expose the mechanisms and extent of subterfuge in published research reports, i.e. EBM.

Regarding terminology, the phrase 'evidence-based', its proven 'viral' potential [29] notwithstanding, is itself misleading. After all, the 'EBM' movement itself effectively repudiated the implications of this label at the point that the concomitant importance of considerations such as patient perspectives and clinical circumstances was acknowledged [45,46]. For reasons to be addressed in the second part of this commentary, we much prefer the phrase 'scientifically informed' to 'evidence-based'. We suggest that this addresses a number of central issues of the dilemma implicitly posed by the article of E-P/H. In any case, whether health care is to be 'based on' or 'informed by' clinical research, it is health care, not the fruits of clinical epidemiology, that is either erroneously founded upon or misinformed by conflicted and biased research.

The evolution of research and health care in the clinical trial era

We have concluded that the proper subject of our inquiry, and of E-P/H's concern, is not 'EBM' but rather the impact of the clinical research enterprise on the health care system. Figure 2 illustrates this as an evolving process. The spiral plot reflects a common, evolving, body of clinical research that informs the full array of health care-research interfaces. The historical antecedents of clinical epidemiology and clinical research go back up to 200 years [22]. However, we start the spiral at a point that many perceive to represent the modern historical dawn of the clinical trial era. In 1962, the Kefauver Amendments in the United States, following on the heels of the famous thalidomide scandal [47], enacted revisions in the US Federal Drug Administration protocol for evaluating new drug applications that required demonstration of both efficacy and safety for such applications to be approved. It was now necessary for a manufacturer to submit data from clinical trials as part of the documentation necessary for approval to market new products, or old products for new clinical uses. This in turn shaped the environment within which Cochrane, 10 years later, could call for an accessible assemblage of all clinical trials, and the concept of systematically using trial results to inform health care policy, clinical guidelines and medical education could emerge.

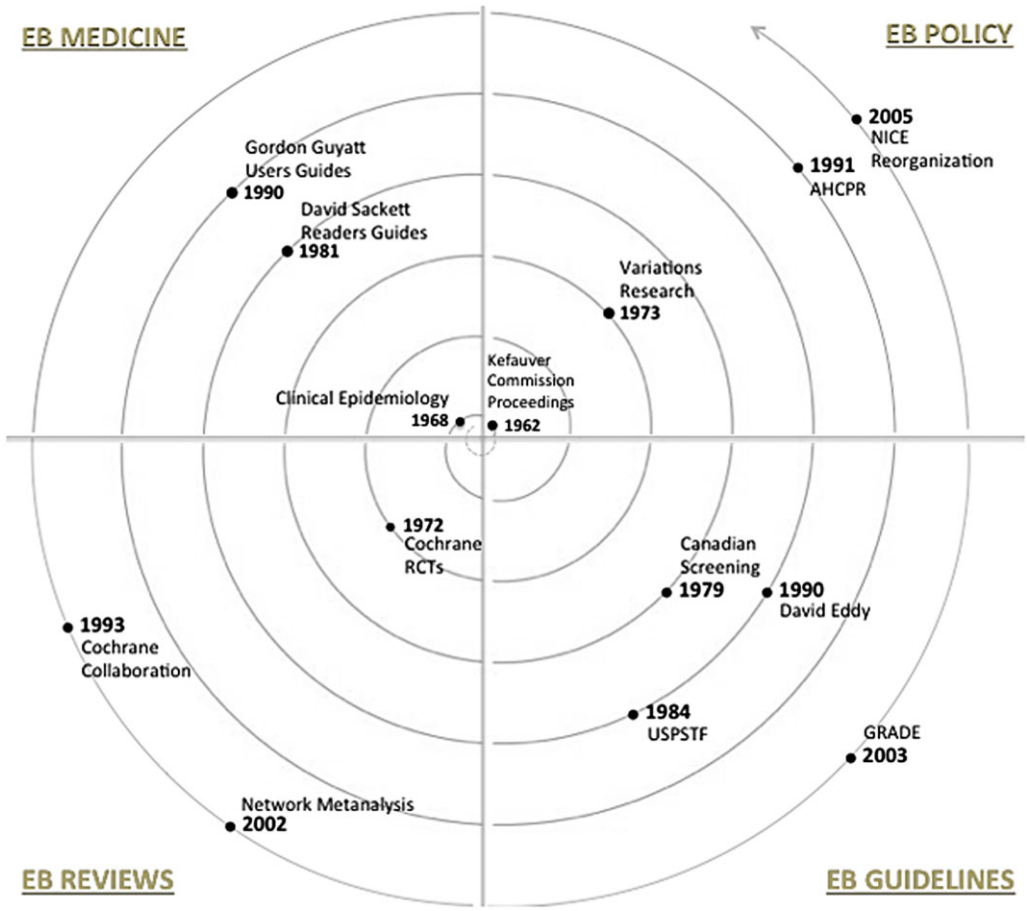

Figure 2 Illustrating the common body of clinical research that feeds all phases of the research/health care interface. The point of origin is the 1992 shift in requirements for new drug application approval by the US Federal Drug Administration that took place in 1962 in the wake of the thalidomide scandal. AHCPR: US Agency for Health Care Policy and Research, currently Agency for Healthcare Research and Quality (AHRQ); NICE: National Institute for Clinical Excellence; UK National Health Service; USPSTF: United States Preventive Services Task Force.

If research is to be considered a source of nourishment to health care, then an unscrambled version of E-P/H's thesis might be stated as a concern that poisoned food is being fed to the system despite the best efforts of EBM to mitigate researcher and sponsor bias. E-P/H propose a number of approaches to 'detoxification' of the research 'food supply', many of which are already in effect. For example, the requirement on the part of major journals of prospective trial registration as a prerequisite to publication has been in force since 2005 [48]. Furthermore, trial registration is strictly enforced by European central trial registries, a reality that has made possible striking and irrefutable documentation of selective publication of negative trials as well as of their inclusion in systematic reviews [49]. E-P/H call for an increase in independent research and the establishment of independent bodies to set research priorities. This process is well under way with the establishment of the US Patient Centered Outcomes Research Institute (PCORI), a funding agency that includes the patient voice in the process of setting research priorities [50]. US based, PCORI entertains competitive funding applications from the international research community to the extent that they meet required specifications. The initiative is young and it is by no means certain that PCORI-sponsored research will ultimately fare better than that sponsored through traditional channels with respect to meaningful uptake and use.

As already noted, E-P/H omit perhaps the most important solution. Namely, educational efforts along the lines of those abundantly offered by the EBM movement can serve to immunize consumers of research to toxic effects of subterfuge and bias. Others among E-P/H's recommendations are impractical or misguided. For example, they suggest that researchers should be rewarded for the quality of their studies but not their results, implying that researchers are responsible for publication bias. In fact, the suppression of negative trials regularly takes place on the level of the research sponsor, not on the level of the journal [15]. Hence, publication bias has little to do with rewards for researchers or lack thereof. Furthermore, within academic medical centres, researchers are rewarded with promotion for landing large research grants, which are awarded on application merit. The quantity of authored publications may well influence their competitiveness. However, this has little to do with the direction of reported results. E-P/H suggest that evidence rating schemes such as those used in the GRADE system [51] be modified to provide

for automatic rating down of evidence drawn from industry-funded trials. This would introduce an arbitrary element into the process of evaluating quality of evidence and would undermine the credibility of such rating schemes as commitments to evaluation of methodological rigor.

Returning to our metaphor of clinical research as food and its successful dissemination as nourishment, rather than E-P/H's proposed remedies for a poisoned food supply, we suggest that a much more challenging issue must take priority, namely, the general failure of the research enterprise to make it past the pylorus. That is, starvation is a more serious threat to health than poisons for which antidotes exist. The bottom of Fig. 1 illustrates what has been referred to as a 'translational block' in health care [52]. Its content is the apparent discordance between the results of clinical research and their utilization. Clinical practice guidelines remain underutilized [53,54] despite strenuous efforts to make them more trustworthy [31]. Decision support instruments, designed to facilitate the use of information from clinical research in clinical decision making, are similarly ignored [55]. Finally, and perhaps pertinent to the thesis of E-P/H, training in EBM generally fails to change practitioner behaviour [56].

The meaningful use of research in health care

Before considering causes and solutions with respect to the perceived failure of the health care system to adequately respond to clinical research, we need to ask what is meant by the 'use' of such research. For some time, the issue of inadequate use of research has been a major concern across a broad range of disciplines including health care. It was addressed 35 years ago in a report commissioned by the US National Research Council [57]. A more recent report, from a different committee operating under the same auspices, concluded that little progress had been made in the interim [58]. Despite their lack of demonstrated impact, these reports usefully highlight several important aspects of the concern. In particular, they pose the issue: what does it mean for research to be used? Weiss identified a multiplicity of possible meanings in the course of the 1978 report [59]. Of these, simple instrumental use within a decision making, problem-solving context conforms to the simplified framework characteristic of an 'evidence-based' construct. However, such use is not necessarily simple. For research, be it a via single trial or a body of work, to have decisive impact on a decision, be it in the context of policy making, a clinical guideline or the care of an individual patient, a formidable set of requirements must be met. For example, the research must address all available alternatives, the contexts and circumstances must be aligned and there must be no overriding considerations stemming from values, costs or availability. However, other potential uses of research are possible beyond the instrumental. What Prewitt *et al*. [58] call 'conceptual use' corresponds to consideration of research within more complex contexts. This may involve matters of defining and understanding problems, context and the terms that will ultimately shape subsequent decision making. Such potential use also applies when so-called complex interventions [60] are at issue, a setting in which simple, instrumental choices are not applicable. As the health care system increases in complexity, the number of available options multiply and conceptual rather than simple instrumental use of research begins to dominate, even within the context of decision making.

If the use of clinical research in health care cannot be reduced to simple choices between clinical options, then a consequence is that simple audits of utilization no longer constitute valid metrics of such use, that is, they do not validly estimate the extent that research is being used effectively throughout the system. Returning to the thesis of E-P/H, by not specifying an assumed mission of EBM, they forfeit the use of any possible metric of evaluation of success or failure in achieving it. We suggest that what is needed is a metric of use, as well as a viable way of understanding non-use, of research in health care.

Probabilistic/ empiricist versus ontologic/realist interpretation of research

The two modes of research use mentioned above fall, at least roughly, into two loosely defined domains of knowledge. Tanenbaum [3], drawing from Wulff [61], characterizes these as 'realism' and 'empiricism'. (Strictly speaking, one might better choose the term 'positivism' or 'neo-positivism' to characterize the second domain [62].) Both modalities are abundantly reflected in the health care literature. The empiricist, or neo-positivist, mode is characterized by the familiar probabilistic stance of interpretation of clinical trial results with emphasis on point estimates of outcome and confidence intervals around them [63]. Estimates are derived from summary data gathered across study populations, either from a single study or, via meta-analysis, from groups of studies judged sufficiently similar to justify the assumption that they are measuring a common effect. An 'evidence-based' approach to policy and decision making advises that, if the point estimate is sufficiently extreme and the confidence intervals around it sufficiently narrow, the decision is made by the evidence most of the time and for most patients, irrespective of whether the context involves health care policy formulation, clinical guidance or the care of an individual [33]. To be sure, proponents of the probabilistic view emphasize that values and preferences, as well as costs and resource use, must be taken into account in the course of an 'evidence-based' appraisal. However, these parameters are themselves to be treated in the same fashion as trial information, that is, as probabilistic estimates, even though not necessarily based upon quantitative studies [33].

The alternative, 'realist', approach to research evidence, which Tanenbaum refers to as 'deterministic' [3], is based upon different premises than the empiricist view and seeks to understand the processes within which decisions are made and choices lead to outcomes. Rather than taking the empirical observation as primary ('evidence-based') and adding probabilistic estimates of other determinants to it, the realist takes the social process itself as primary and draws on empirical observation as it is perceived to be relevant ('scientifically informed'). The realist approach stresses the interpretive aspect of research evaluation within the social process within which evaluation takes place. Based on her own observations of clinical practice on an internal medicine ward some two decades ago, Tanenbaum concluded that the process of clinical care is largely interpretive, involves storytelling and that probabilistic thinking introduced an foreign, quantitative, element into an inherently qualitative, narrative, process [3]. Tanenbaum

also considers the probabilistic use of clinical research in the health policy arena, particularly citing the work of the Dartmouth school [36]. She identifies the reflection back of outcomes research into the domain of the individual practitioner in the form of policy prescriptions and mandates [3,64], and finds this to be problematical.

Tanenbaum's formulation is compelling insofar as incompatible modes of use of research might account, at least in part, for the apparent failures of uptake of clinical trial results across the four streams represented in Fig. 1. Our figure further facilitates the identification of disconnects and 'short circuits' of the sort suggested in her reports. These easily arise, given that a common body of clinical research serves as the source of such information for all streams (Fig. 2). For example, clinical guidelines, aimed at practitioners and their patients, may be seriously undermined with respect to use by their intended target, when they are adopted, or even perceived likely to be adopted for use on the health policy level. This was dramatically illustrated by the turmoil that occurred after the United States Preventive Services Task Force (USPSTF) released revised recommendations for screening mammography in 2009 [65]. Relaxation of recommendations for younger women, using wording intended to reinforce interaction and partnership between women and their clinicians, was seized upon by political voices who proceeded to propagate fears of imminent denial of insurance coverage for screening elected for women under 50 years of age. This example serves to illustrate that the intended social context of use, not the raw content of research results, needs to guide the process of assimilation of such results into policy and practice, a point not always heeded by even socially well-meaning governmental administrations. Figure 2 illustrates the distinction between clinical guidance and health policy development. For example, the USPSTF and the NICE of the United Kingdom reside in different quadrants of the figure. Whereas the first agency is made up of primary care practitioners and methodologists and ostensibly produces guidelines for use within such practice settings, the second produces reviews and recommendations for use by the British National Health System in determining policy for coverage and availability [66]. The approach to evidence synthesis used by USPSTF and NICE is similar and comparably rigorous [67–69], NICE having recently switched over to the GRADE system [34]. Both draw on a common body of clinical research and perform systematic reviews on the questions to be researched. However, the intended use and purpose of their recommendations are importantly different, and hence the context of use of the research they consider. It is perhaps unfortunate that the GRADE Working Group appears to invite and encourage the use, not only of evidence summaries but also of recommendations, jointly for clinical guidance and for health care policy [33], the two contexts reflecting quite different social processes, constituencies and stakeholders. It is in keeping with a positivist, probabilistic conceptual framework to downplay social process and interpretation in favour of an approach to research evidence that considers interpretation to be largely self-evident [3].

Translation and brokerage versus social constructivism

Returning to the dilemma facing the relationship between clinical research and the health care system, that is, the apparent drastic underutilization of the former by the latter, let us consider the range of possible remedies. Prewitt *et al*. [58] summarize several models of approach to closing the gap. In the simplest form, the so-called translational model, information from research is repackaged and framed in language to which receivers and potential users of research can better relate. Decision support tools, which may be aimed variously at practitioners, patients or both, are a form of translational instrument. Unfortunately, systematic reviews of use of these instruments have been disappointing [55]. One possible reason for such disappointment may be that the approach to developing such instruments has largely been confined and subordinated to a probabilistic approach to interactions and decision making and to oversimplified notions of information exchange between protagonists. Advocates of use of decision support in the context of shared decision making propose a largely epidemiologically driven set of criteria for appropriate use, specifically prescribing as a precondition the need for 'equipoise', that is, perception of equal probabilities of benefit and harm ensuant to a health care choice [70]. The GRADE system [71] specifies that shared decision making be used for 'weak', but not for 'strong', health care recommendations [33]. In what might be called 'epidemiological' or 'probabilistic' sequestration, 'strong, evidence-driven', recommendations call for unidirectional communication; 'weak' recommendations, defined by epidemiological 'equipoise', call for bidirectional communication and no situations call for unrestricted interactional, or relational [72], processes. Within this framework, patient and stakeholder preferences and values are 'respected' [70]. However, the role of interpretive, social, processes is held to a minimum. The limited use [55] in social settings of instruments developed from within this conceptual framework is therefore not surprising.

Prewitt *et al*. [58] identify 'brokering' as an alternative approach to closing the gap between research and application. Brokers facilitate use of research perceived to be relevant in specific settings in more active and dynamic ways than that which characterizes simple translational approaches. A substantial cottage industry has developed around the perceived need for research brokerage, which, in the United States, involves government agencies such as the National Research Council (NRC), the IOM and funding agencies such as the Agency for Healthcare Research and Quality, as well as a myriad of private sector think tanks and other organizational types [58]. A broad spectrum of disciplines, including social sciences and law in addition to health care, are the subject of research brokerage. One disadvantage of the approach is that such external approaches ultimately multiply the cost to society in direct and indirect ways. Another is that such approaches may be ineffective [73,74], or may be limited in usefulness to settings in which the importance of consideration of research is already culturally ingrained [73].

A third approach acknowledged in the NRC report on research use is termed an 'interaction model'. It potentially escapes the confines of the positivist, epidemiologically driven framework in which the issue of use has largely been enmired. The category does not embrace a single universally understood methodology or philosophy but rather traverses a spectrum, which extends from realism [3,75–77] to approaches that even more explicitly reject the positivist premises of epidemiology and most clinical research [78–80]. Some approaches to 'knowledge translation' fall into this eclectic category [81]. We have previously labelled this approach

'constructivism' in a sense intended to reflect the relational outlook of the Brazilian educator Paolo Freire [62,82]. A defining characteristic of constructivist cultural approaches to the use of research is that the research itself is subordinated to the social process within which it is understood and interpreted. It is not simply 'implemented'. Within such an environment, stakeholder values, preferences and perspectives rule, in contrast to the epidemiologically driven framework in which they are merely 'respected'.

Realist approaches to health care and health services research have begun to be encouraged [77] and demonstrated. The realist approach to research conforms to the 'deterministic' model described by Tanenbaum [3] and places emphasis upon understanding the processes at work within a complex health care environment [75]. Approached rigorously, highly correlated, potentially causal, relationships are identified within the process, which are then subject to hypothesis testing [77]. However, although principles of causality are recognized, the pursuit of simple probabilistic solutions to health care choices are de-emphasized. Realist approaches to the enhancement of research uptake and use are particularly popular within the context of evidence-based practice initiatives on a systems level [83]. Such efforts draw on tools and approaches discussed previously, including brokerage and facilitation, use of communication instruments and other approaches developed under the knowledge translation rubric [84].

Organized approaches to research sponsorship, currently underway in the United States, are potentially aligned with a constructivist orientation. The previously mentioned US PCORI [50], established under the legislative auspices of health reform, is committed to sponsorship of research focused on questions of concern to patients and their families. The PCORI protocol calls for patient to serve as part of the investigator team and to be involved in the design and execution of clinical studies. The PCORI vision is promising as a means of strengthening the relationship between research and patient-centred aspects of the health care system.

A learning health care system

Over the past several years, an important broker for use of research in health care, the US IOM, has emerged as a major sponsor of the concept of a 'learning health care system (LHS)' [85–89], a construct which in turn tends to affirm our formulation of the issue of whether the proper mission of utilization of clinical research in health care is succeeding or failing. The LHS, based upon the concept of a learning organization [90], envisions seamless interaction of all levels of health care, from policy to delivery including the patient and consumer voice, within which the use of evidence from external research as well as from practice-based sources, is routinely tapped and used for purposes of continuous improvement of services and of clinical outcomes. The IOM vision places important emphasis upon practice-based evidence (PBE) [91], that is, the use of information drawn directly from the health care system, as opposed to externally funded research. The accumulation and use of PBE will be reinforced through the development of a national network of databases, 'PCORnet', currently being developed under the auspices of PCORI [89]. Practice-based evidence, although disadvantaged as a means of deriving probabilistic estimates of comparative effectiveness of clinical options under research conditions, has the advantage of offering information, including outcome data, from the actual settings in which health services are delivered, and in a much more timely fashion than is possible with conventional clinical research [92]. The importance of PBE has been long recognized by the developers of multidisciplinary evidence-based practice models [93].

The LHS vision potentially encompasses relational principles, including patient engagement in all phases of the health care system [88], amidst a comprehensive understanding of health care and organizational functioning. Hence, it calls for an environment conducive to constructivist social process and is promising as a framework for maximizing effective use of information. One pioneer of organizational theory is Ikujiro Nonaka, a Japanese theorist identified with the thinking of Polanyi [94], Varela [95] and through the latter, Merleau-Ponty [96]. Reviewing the spectrum of organizational theory from the standpoint of creation and use of knowledge [97], he identified potential weaknesses in the conceptual framework of organizational learning as reflected in standard sources [98]. Specifically, Nonaka perceived that such approaches fall short insofar as they do not address the tacit operational knowledge and understanding of middle management and front line personnel within an organization. His concept of organizational knowledge creation emphasizes the importance of transformations between tacit and explicit knowledge. Nonaka suggested that overlooking such processes fails to maximize internal, implicit, organizational knowledge capacities and risks overdependence upon external resources and change agents [97]. The costs of external knowledge brokering and facilitation might well constitute examples illustrating Nonaka's concern.

Potential theoretical limitations notwithstanding, the concept of learning organizations within a learning health care system coheres with the integrated framework of research use presented in Figs 1 and 2. Such organizations embody policy development, reviews and analyses of information and data, clinical guidance, and educational initiatives, all as essential ingredients of maximizing the value of research and of delivered services. It is this perspective that has redefined the terms on which debates about the relationship between science, research and social process need to be addressed and corresponding missions within health care defined.

Summary – filling the epistemological void

Although E-P/H reveal themselves to be uninformed in specific areas relevant to their thesis, it is the thesis itself that emerges as poorly defined and ambiguous in ways that cannot be explained by lack of information. Their confusion usefully reflects a general prevalence of fuzzy thinking within a broad range of literature addressing aspects of the use of research within the health care system. Hand-wringing about the tendencies of both researchers and research sponsors to exaggerate and inflate the apparent importance of research results and the effectiveness of products, particularly when ample remedies have been and are being put in place, seems misdirected. Confusion of 'EBM' with the research enterprise that it was developed to critique, and commiseration regarding the failure of a mysterious and undefined mission, is a hollow evasion of the emerging challenges within a rapidly evolv-

ing health care environment. It may seem to constitute a comfortable stance to take when transcending the boundaries of a flawed epistemology is perceived to be a bridge too far. To his credit, Howick recognizes that the design-based 'hierarchy' of evidence, long a bulwark of the epidemiological foundations of EBM, is no longer viable [7]. However, his unqualified defence in the same source [7] of the even more challengeable hierarchy of knowledge proposed in the original 1992 EBM manifesto [1] is the skeleton in the closet of E-P/H's discussion of EBM's supposedly failed mission.

Notwithstanding the fact that durable changes in practitioner behaviour lay beyond the scope of its worldview, EBM, as an educational movement, accomplished its mission by clarifying, codifying and disseminating principles of methodological evaluation of research and by proving that they could increase research literacy on the part of educators and clinical learners. Aside from product development and career advancement, the mission of research is ultimately determined by social processes, processes that are unavoidably dominated by judgments, interpretations, political and intellectual agendas. The successful engineering of a health care system to maximize the contribution of research to health will need to be founded on these processes and to be based upon appropriate philosophical foundations.

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