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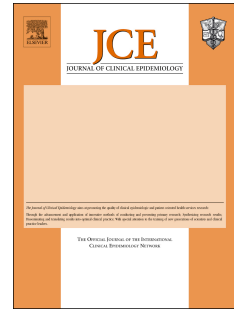
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## **Evidence-Based Medicine Has Been Hijacked: A Report to David Sackett**

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**Abstract**

This is a confession building on a conversation with David Sackett in 2004 when I shared with him some personal adventures in evidence-based medicine (EBM), the movement that he had spearheaded. The narrative is expanded with what ensued in the subsequent 12 years. EBM has become far more recognized and adopted in many places, but not everywhere, e.g. it never acquired much influence in the USA. As EBM became more influential, it was also hijacked to serve agendas different from what it originally aimed for. Influential randomized trials are largely done by and for the benefit of the industry. Meta-analyses and guidelines have become a factory, mostly also serving vested interests. National and federal research funds are funneled almost exclusively to research with little relevance to health outcomes. We have supported the growth of principal investigators who excel primarily as managers absorbing more money. Diagnosis and prognosis research and efforts to individualize treatment have fueled recurrent spurious promises. Risk factor epidemiology has excelled in salami-sliced data-dredged papers with gift authorship and has become adept to dictating policy from spurious evidence. Under market pressure, clinical medicine has been transformed to finance-based medicine. In many places, medicine and health care are wasting societal resources and becoming a threat to human well-being. Science denialism and quacks are also flourishing and leading more people astray in their life choices, including health. EBM still remains an unmet goal, worthy to be attained.

This conversation with David Sackett started in 2004, at a retreat somewhere in the English countryside, when we met as part of the International Campaign to Revitalise Academic Medicine (ICRAM). ICRAM was an ambitious project by well-meaning people to change academic medicine [1]. I suspect that we failed magnificently, in due proportion to our utopian ambition. I shared with David some personal adventures in evidence-based medicine (EBM). There he was, a master listener, a wonderful living mirror to talk to. Those who did not have the chance of interacting with him may still benefit from the excellent series of papers on mentoring that he wrote with Sharon Straus [2-5]. As I described my trials and tribulations, it became clear that somehow he was already familiar with them. Apparently, he had already lived something similar, often worse, in his own career [6]. Over the following 12 years, this conversation has continued to grow in my mind, adding new chapters to it, as I have accumulated more defeats. Defeats that I have wanted to share with David Sackett even in absentia.

“David, I am a failure. I had long heard about your legacy: at age 32 you had been recruited to a rather unknown medical school in a small city built on the shores of a lake to start a department of clinical epidemiology and biostatistics, the first of its kind in the world. Three decades later I was one of those dangerous 32 (standard deviation +/- 6) year-olds who you had inspired. At the age of 32, I was offered to lead a department of the same kind at an even more unknown medical school in a smaller city built on the shores of a much smaller lake. Being a dual citizen, a weird non-evidence-based prerequisite for getting a faculty position in a public university was to serve 6 months in the army. During these 6 months, I wrote lots of desperate poetry, some papers, and a 350-page book on “Principles of Evidence-Based Medicine” in Greek. You are largely to blame for this latter composition. Along with Gordon Guyatt and other

colleagues at McMaster, you had started that “evidence-based medicine” [7,8]. It had haunted me since the early 1990s when I had heard about it from the late Tom Chalmers and Joseph Lau.

Computers were not allowed on boot camp, but I secretly sneaked in a small Pentium palmtop. I was working in the physician on call room in a submarine and frigate base in the island of Salamis. Even though history is not a randomized trial, causal inferences are (spuriously?) made that victory in the naval battle of Salamis had allowed freedom of rational thought to flourish in the classical age - perhaps a forerunner to the freedom of thought that fostered EBM. Several window panes were missing in the on call room, but hopefully Greece is not as freezing as Ontario – most of the time. One broken window actually had a nest of wasps attached, so one could often find an occasional wasp in the bedsheets. We hospitalized mostly young recruits who had gone crazy during their military service. One of them was roaming outside playing precariously with a lighter whenever it was windy. He was eager to put the surrounding forest of pine trees on fire, burn down our 19<sup>th</sup> century neoclassical hospital building and get revenge for losing his mind. Sometimes, I was thinking whether people see EBM as an incendiary risk, and EBMers as lunatics threatening to burn to the ground the dilapidated neoclassical building of medicine.

I had come from major US institutions where I had sadly realized that almost nobody cared about EBM. Yet, now I was in continental Europe where even fewer people cared about EBM. My first grant application was not even rejected. It went to an august reviewing body and I still have not heard back from them, apparently it is being reviewed over 17 years now and counting. Many of the prestigious reviewers must be dead by now. My subsequent EBM-related applications were typically promptly rejected, although I did manage to get funding over the years – perhaps for my most dull ideas.

EBM met with substantial resistance in the 1990s and 2000s. Even in USA, the mecca of biomedical research, EBM and any serious biomedical research that may help intact humans was largely unwanted. As a clinical research fellow, I remember that every week we were waiting to hear whether the Agency for Health Care Policy and Research (AHCPR, which subsequently became AHRQ) would be axed. The Agency had hurt the interests of some powerful professional surgical society: one of its guidelines threatened the indications for an expensive and possibly largely useless surgical procedure. AHCPR/AHRQ survived, but has always had to fight valiantly for its existence since then. EBM is widely tolerated mostly when it can produce largely boring evidence reports that are shaped and endorsed by experts. Many years later, the Patient-Centered Outcomes Research Institute (PCORI) was launched, an equally valiant effort to cover some of that vast space. It was also restricted by a mandate not to deal with cost-effectiveness of interventions. I was asked to participate in its Methodology Committee along with great colleagues. I contributed far less than anyone else to the effort before deciding to quit out of shame for my lack of contribution. Most of our tasks seemed to require experts rather than evidence. More than 7 billion of people would be better qualified than me to lead expert-based activities.

But let me flash back to Europe and the late 1990s. When I was appointed as faculty, I felt even more of an outcast. At faculty committees and assemblies and prestigious societies in continental Europe, when some senior academic opinion leaders wanted to spit and curse, they would use instead the words “meta-analysis” and “EBM”. When I published a story in the Christmas BMJ on how physicians are treated by the pharmaceutical industry with free lunch vacation with full entertainment in the Arabian peninsula [9], a powerful politically-connected syndicalist doctor in Athens wrote to the medical society asking for my exemplary punishment

and revocation of my medical license. He also attacked me personally at the board of directors of the national disease control center where I was vice president. He entered one day the board room and said that he cannot co-exist with a person of such exceptionally low moral standards. No one defended me, but eventually he did not have his way. I feel sorry that he had to co-exist with such a horrible person like myself.

However, things got far worse when EBM became more successful and recognized in many places beyond Canada. The same people who were previously spitting when mentioning “EBM”, started using the very same term to buttress their eminence-based medicine claims to prestige. Several senior people started to ask me to work with them, hoping that they would publish papers in major journals. Saying “no” and trying to stick to high standards for my work bought me even more enemies, including leaders of academia, politics (of the entire corrupted range of left-to-right spectrum) and academic politics. Even the syndicalist who had once tried to annihilate me re-approached me: “John, we all know that you are the best scientist in the country. Why don’t we work together? You know how successful I am.” He presented a long list of his power attributes and connections. The catalogue was stunningly impressive. Then he added: “the only thing that I lack is major publications in top impact journals. So, here is what we will do: I will give you power and you will put my name in major evidence-based publications.”

I hate having power, so obviously I declined. I have always preferred to work with the young and the powerless. But this made even more powerful people even angrier with me. A senior professor of cardiology told a friend of mine that I should not be too outspoken, otherwise Albanian hit men may strangle me in my office. I replied that they should make sure to get correct instructions to my office – turn left when they come up the stairs. I would feel remorse, if the assassins entered the wrong office and strangled the wrong person.

Now that EBM and its major tools, randomized trials and meta-analyses, have become highly respected, the EBM movement has been hijacked. Even its proponents suspect that something is wrong [10,11]. The industry runs a large share of the most influential randomized trials. They do them very well, they score better on “quality” checklists [12] and they are more prompt than non-industry trials to post or publish results [13]. It is just that they often ask the wrong questions with the wrong short-term surrogate outcomes, the wrong analyses, the wrong criteria for success (e.g. large margins for non-inferiority) and the wrong inferences [14-16], but who cares about these minor glitches? The industry is also sponsoring a large number of meta-analyses currently [17]. Again, they get their desirable conclusions [18]. In 1999 at the closing session of the Cochrane Colloquium in Rome, among the prevailing enthusiasm of this benevolent community, I spoiled the mirth with my skepticism. I worried that the Cochrane Collaboration may cause harm by giving credibility to biased studies of vested interests through otherwise respected systematic reviews. My good friend, Iain Chalmers, countered that we should not worry – plus there were many topics where the industry had not been involved. He mentioned steroids as one example. It was not very reassuring. Now even the logo of the Collaboration, the forest plot for prenatal steroids, has been shown to be partially wrong due to partial reporting [19] - let alone reviews of trials done with vested interests from their very conception.

I am not against the industry, quite the opposite, entrepreneurship is crucial for translation, development and growth. However, corporations should not be asked to practically perform the assessments of their own products [20]. If they are forced to do this, I can't blame them, if they buy the best advertisement (i.e. “evidence”) for whatever they sell.



Clinical investigators flock to try to get co-authorship in multicenter trials, meta-analyses and powerful guidelines to which they contribute little of essence. Vested interests dictate pre-emptively large segments of the research agenda and its evidence-based aura [21,22] which is further propagated in professional societies and large conferences [23]. Many leaders and members of powerful professional societies and academies and other august bodies grow out of this system. It is sometimes difficult to tell whether a superb CV with a lengthy publication list reflects hard work and brilliant leadership or the composite product of dexterous power game networking, gift authorship [24], and excellence in the slave trade of younger researchers.

Having worked in many different clinical fields, my identity was often mistaken. Some CROs recruiting patients for industry trials believed that I was a clinic chief or chair in cardiology, rheumatology, or other clinical fields. I would get invitations in my fax machine running “Dear Professor Ioannidis, we know that you are a great interventional cardiologist and your clinic is one of the best. Would you be interested to participate in the X trial...”. For fun, one day I called back the contact number. I mentioned that I had received that kind invitation and wanted to find out how I could join the research. The person at the other end of the phone line promised me authorship in the randomized trial; the more patients I could recruit, the better my authorship position. I asked to see the protocol and comment on it. The answer was clear and immediate “Oh, the protocol, why should you worry about the protocol? The sponsoring company has taken care of the protocol already and will also take care of writing the paper. You don’t need to worry about that minor stuff. You shouldn’t waste time with the protocol or editing drafts. We will put your name as an author on the papers, no worries. This is what all prestigious clinical researchers do.”

While many clinicians adopted this *forme fruste* EBM and all the accompanying industry funds, bench scientists absorbed almost all the national and federal research funds in both Europe and the USA in the meanwhile. David, you have stated this clearly: “The issue is that basic medical scientists have hijacked the granting bodies and have erected research policies that place greater value in serving their own personal curiosities than in serving sick people.” [25] Of course, those who are the most successful in grantmanship include many superb scientists. However, they also include a large share (in many places, the majority) of the most aggressive, take-all, calculating managers. These are all very smart people and they are also acting in self-defense: trying to protect their research fiefdoms in uncertain times. But often I wonder: what monsters have we generated through selection of the fittest! We are cheering people to learn how to absorb money [26], how to get the best PR to inflate their work [27], how to become more bombastic and least self-critical. These are our science heroes of the 21<sup>st</sup> century.

With clinical evidence becoming an industry advertisement tool and with much “basic” science becoming an annex to Las Vegas casinos, how about the other pieces of EBM, e.g. diagnosis and prognosis and individualizing care? I have had great excitement about the prospects of -omics, big data, personalized medicine, precision medicine, and all. Much of my effort has been to put together these efforts with rigorous statistical methods and EBM tools. But I am tired of seeing the same over-rated promises recast again and again. For example, several years ago I gave an invited lecture at a leading institution on the danger of making inflated promises in personalized medicine. Right after my talk, everybody rushed to hear the launch of a new campaign, where the leader of the institution singled out this unique historic moment: that institution would single-handedly eliminate most major types of cancer within a few years. Several years have passed and none of these cancer types have disappeared. I recently tried to

find the name of that campaign online, but realized that this institution has launched many similar campaigns. Which among many was the unique historic moment that I happened to be at? Multiply this by thousands of institutions, and there are already millions of unique historic moments where cancer was eliminated. Same applies to neurological diseases and more. I don't understand why academic leaders and politicians need to make such self-embarrassing announcements now and then.

Claims are even made that with new big data the scientific method is obsolete: petabyte data will replace the scientific method [28]. I apologize for being so old-fashioned, but I believe the scientific method is alive and well and will remain so, regardless of amounts of data. Data will be astonishingly more plentiful in a few years compared to the current era which will then be seen as a period of data dearth. We will still need the scientific method to make sense of data.

As for epidemiology, risk factors for disease are becoming more dangerous than ever. By this, I mean two things. First, strong risk factors with unquestionable evidence like smoking are killing now globally more people than ever. Second, instead of dealing with these major public health risks, the production of spurious, false-positive or confounded putative risk factors is more dangerous than ever. Jumping from correlation to causation [29], data dredging is called causal evidence and fuels guidelines. Most data and protocols are not shared. Most studies have no pre-specified protocols and analyses anyhow. While team work and large consortia have improved enormously the quality and reproducibility of work in some fields of epidemiological investigation, some others have promoted mostly massive gift authorship. Some professional co-authors will probably die but will continue to have their names placed on new publications several years posthumously. The submitting author may forget that they are long dead, buried among dozens of automatically listed co-authors. On the other hand, some opponents of risk

factor epidemiology are even worst: even more aggressive and even more insolent corporations try to minimize and negate the risk of their products [30]. One is caught between Scylla and Charybdis trying to navigate these waters. Sometimes I get invitations by lawyers to testify for the safety of products. I decline them all. But then, I see excellent colleagues in epidemiology flocking in opinion pieces with over 120 authors [31] trying to argue that risk factor guidelines are totally impeccable, opposed by other excellent colleagues who don't think so [32]. I cannot take sides in debates where numbers of co-authors are counted as evidence. Science is not about vote counting and signing petitions, it is (or should be) about evidence and its cautious interpretation.

Many of my best allies over the years have been practicing physicians who know firsthand what the major problems are and what really matters for health and disease. David, you defined and clarified EBM admirably when you expressed this duality: "It's about integrating individual clinical expertise with the best external evidence" [33]. But that clinical expertise component is in crisis. In most developed countries, clinicians are under tremendous market pressure. Most discussions in department meetings are about money. One can sense the pressure to deliver services, to capture the largest possible market share (a synonym for "patients"), to satisfy customers (synonyms for "humans"), to get high satisfaction scores, to charge more, to perform more procedures, to tick off more items on charge forms. (As an aside, a nice joke is that these charge-driven electronic health records are then used for research). This is not what I thought medicine would be about, let alone evidence-based medicine. This is mostly finance-based medicine. I won't blame anyone. These physicians have no other option. This is how the world works, they are fighting to keep their jobs. Yet, how likely is it that physicians will design studies whose results may threaten their jobs by suggesting that less procedures, testing,

interventions are needed? How likely is it that, if they do design such studies, they will accept results suggesting that they should quit their jobs? How many are willing to fully resign from the field where they have built a name, as you did twice in your career, David [34,35]? Is EBM doomed to be heartily accepted only when it leads to more medicine, even if this means less health [36,37]?

David, I was astonished by your sense of humility and self-knowledge when I heard that you decided to undergo residency training again to refresh your clinical skills when you were already a full professor. Several years ago, I decided not to practice medicine any longer. I might have caused more harm than good. I could not even think of remedying this by repeating training. Re-training on how medicine is practiced today might make me worse. In some settings, we are close or past the tipping point where medicine diminishes rather than improves well-being in our society. Some truly excellent and committed physicians certainly continue to make positive contributions to health, improve lives, and save lives. However, with 20% of GDP being spent on health and health care so inefficiently, with such limited evidence or with conflicted evidence, medicine and health care can become a major threat to health and well-being.

I felt that I had to take sides in this evolution. This is why I thought that prevention is a great idea, trying to find ways to make people to improve their health, wellness, and well-being at large [38]. After all clinical epidemiology was first defined as “the basic science of prevention” [39]. Yet, I am aware that prevention (e.g. unnecessary screening) can also sometimes harm more people than therapeutic medicine.

There are also so many quacks ranging from television presenters and movie stars turned into health trainers [40], and pure science denialists (e.g. climate, HIV, vaccine denialists, and religious fundamentalists) that one has to tread carefully. We should avoid a civil war on how to

interpret evidence within the health sciences when so many pseudo-scientists and dogmatists are trying to exploit individuals and populations and attack science. However, too much medicine and too much health care is already causing harm. We need to revert this and be frank. In my inaugural speech for the chair of disease prevention at Stanford, I told my well-meaning physician colleagues chairing the therapeutic disciplines' departments that if I succeed in my goals to promote health and well-being, they may lose their jobs.

David, I was a failure when we started this conversation and I am an even bigger failure now, almost 12 years later. Despite my zealot efforts, my friends and colleagues have not lost their jobs. The GDP devoted to health care is increasing, spurious trials and even more spurious meta-analyses are published at a geometrically increasing pace, conflicted guidelines are more influential than ever, spurious risk factors are alive and well, quacks have become even more obnoxious, and approximately 85% of biomedical research is wasted [41]. I still enjoy science tremendously, focusing on ideas, rigorous methods, strong mathematics and statistics, working on my weird (and probably biased) writings alternating with even more desperate poetry, and learning from young, talented people. But I am also still fantasizing of some place where the practice of medicine can still be undeniably helpful to human beings and society at large. Does it have to be a very remote place in northern Canada close to the Arctic? Or in some isolated beautiful Greek island where corpses of unfortunate refugees are found on the beach or floating in the water almost every day, as I am writing this commentary, even though no naval battle has been fought? Is there still a place for rational thinking and for evidence to help humans? Sadly, you cannot answer me any longer, but I hope that we should not have to escape to the most distant recesses of geography or imagination. Twenty-five years after its launch, EBM should still be possible to practice anywhere, somewhere – this remains a worthwhile goal.”

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Conflict of interest

ACCEPTED MANUSCRIPT