What is Evidence-Based Medicine? Dr Bruce Hoffman

The term 'evidence-based medicine' (EBM) was first used in 1990 by G.H. Gyatt, a professor from McMaster University Canada, but a broader description of EBM appeared in 1992, when the Evidence-Based Working Group published a new approach to teaching the practice of medicine in JAMA.[1] The article stressed that "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."[2] The article emphasized that this would require "new skills of the physician, including efficient literature searching and application of formal rules of evidence evaluating the clinical literature."[3] Tradition, anecdote and theoretical reasoning based on the basic sciences would be replaced by evidence from high-quality, randomised, controlled trials and observational studies, in combination with clinical expertise and the needs and wishes of patients.[4]

On the Internet, numerous articles discuss other potential definitions of the term 'evidence-based medicine'.[5] Sackett et al. define EBM as "the integration of best research evidence with clinical expertise and patient values".[6] Another definition states that "EBM is nothing more than a process of life-long, self-directed learning in which caring for patients creates the need for clinically important information about diagnosis, prognosis, therapy, and other clinical and health care issues." A further definition suggests that EBM is "an evolutionary progression of knowledge based on the basic and clinical sciences and facilitated by the age of information technology."[7]

Many of the above definitions arose from a BMJ article published in 1996, which stated that EBM is the conscientious, explicit and judicious use of the best current evidence in making decisions about the care of individual patients. The practice of evidence-based medicine involves integrating individual clinical expertise with the best available external clinical evidence from systematic research.[8]

Evidence-based medicine requires asking relevant clinical questions concerning the patient's issues, performing a literature search for relevant research data to support or refute diagnostic and/or treatment approaches, critically appraising the literature regarding its validity and applications, and then implementing one's findings and insights in a clinical setting.

Twenty-five years ago, evidence-based medicine, which involves utilizing the medical literature to effectively guide medical practice, was considered profound enough to be described by the initial authors as a paradigm shift in the way medicine was to be practiced. The authors reported Thomas Kuhn's description of a scientific paradigm as "[a way] of looking at the world that define[s] both the problems that can legitimately be addressed and the range of admissible evidence that may bear on the

[1] Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA 1992; 268: 2420-5.
[2] Ibid.
[3] Ibid
[4] Greenhalgh, T., "Evidence-based medicine: a movement in crisis?" BMJ 2014; 13 June, 348
[5] http://researchguides.uic.edu/ebm
[6] Sackett D.L., et al., "Evidence-Based Medicine: How to Practice and Teach EBM." Edinburgh: Churchill Livingstone.
[7] Doherty, Steve. "Evidence-based medicine: Arguments for and Against." Emergency Medicine Australasia 2005; 17: 307-13.
[8] Sackett, D.L., Rosenberg, W.M.C., Gray, J., Haynes R.B., Richardson W.S., "Evidence-based medicine: what it is and what it isn't." BMJ; 312:71-72.

solution".[9] When defects in an existing paradigm accumulate to the extent that the paradigm is no longer tenable, the paradigm is challenged and replaced by a new way of looking at the world.

Some of the shift toward evidence-based medicine was initiated due to a loss of confidence in the traditional medical model and the studies that had initiated those practices. Larry Dossey M.D. commented on many of the scandals that rocked the confidence of healthcare consumers at the end of the last century.[10] "The uncertainties of medicine are cause for celebration," Dossey wrote. "Modern medicine is losing some of its invincibility. Many of the rules of good health that have guided patients and physicians for decades have taken a beating from which they may not recover. The almost blind allegiance we once had to the treatments offered has been severely undermined by these studies — some of the absolute certainties are no longer as absolutely certain."

First there was the Vioxx drug scandal, in which many people died from heart disease after consuming what were thought to be relatively innocuous anti-inflammatory drugs. Compounding the problem was the fact that this particular drug had been marketed as being relatively safe. Furthermore, evidence emerged that the drug companies had known for some time that the drug had an increased incidence of cardiac side effects, but they had chosen to hide these negative findings to ensure a profit.

In the Women's Health Initiative study,[11] hormone replacement therapy (HRT), specifically Premarin and Provera, once a mainstay of post-menopausal symptom management and considered to be safe, was shown to actually increase women's risk of heart disease, stroke, thrombosis and breast cancer. The risks of increased cardiovascular disease (CVD) and breast cancer were concluded to far outweigh the benefits of osteoporosis protection and colon cancer reduction. Millions of women, to the fan-fare of massive nation-wide news coverage, were immediately withdrawn from hormone replacement therapy as a result of these findings. The sales of these two drugs dropped 50% in one month. The American Association of Clinical Endocrinologists, (AACE), the American Congress of Obstetricians and Gynecologists (ACOG) and the North American Menopause Society (NAMS) recommended HRT use only for short-term symptom control. Later critiques of the study pointed out some bias and manipulation of data, including but not limited to the following:

1) Many women chosen for the study were not in the typical age range for HRT – they were, on average, 12-15 years past the age of menopause and had significant baseline cardiovascular and coronary artery disease (CAD) at the initiation of the study.
2) Approximately 74% of the women included in the study had never used HRT before and were outside the 3-4 year post-menopausal window of opportunity for HRT, in which cognitive and cardio-protection from HRT was maximal.
3) Premarin was the estrogen used in the study. Premarin is a conjugated equine estrogen drug with 50% estrone (known to increase breast cancer risk prior to the WHI study), equilin and equilenin, both of which have unknown activity on human estrogen receptors. The WHI study was not undertaken with human estrogens (E1=estrone, E2=estradiol and

[9] Kuhn, T.S., The Structure of Scientific Revolutions. Chicago, Ill: University of Chicago Press; 1970
[10] Dossey, L., Alternative Therapies Sept/Oct 2002, Vol. 8, No.5 32

[11] Rossouw, J.E.[1], Anderson, G.L., Prentice, R.L., LaCroix, A.Z., Kooperberg, C., Stefanick, M.L., Jackson, R.D., Beresford, S.A., Howard, B.V., Johnson, K.C., Kotchen, J.M., Ockene, J. Writing Group for the Women's Health Initiative. (2002). "Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial." JAMA. 288(3):321-33.

E3=estrone). Premarin is an oral equine-derived preparation and is known to increase liver coagulation proteins, thus increasing the risk of stroke and cardiac events. Transdermal estrogen was not used, which has shown no association with the increased activation of liver clotting proteins. NAMS preaches that there are no randomized, placebo-controlled trials to support the claims of increased efficacy or safety of compounded, bioidentical hormones; however, there is a plethora of studies demonstrating the superior efficacy and safety of pharmaceutical bioidentical hormones over non-bioidentical, synthetic hormones.

4) Progestin was the chosen progesterone preparation. This is a medroxyprogesterone acetate preparation that had already been shown to have an unfavorable effect on lipid profiles prior to the WHI trial.

Much criticism was levelled against the WHI study when the data were placed within a clinical perspective and further studies reached different conclusions. The results of the WHI and the Heart and Estrogen/Progestin Replacement Study (HERS) trial, when reassessed, were shown to not apply to younger women, specifically those aged 50-60. In most of the subsequent studies, there were no cardiovascular deaths among 6,000 women on HRT, as compared to several deaths in the placebo group. [12] There was overwhelming evidence that the anti-atherosclerotic effect of HRT depended on the time of initiation and that early initiation was protective.

With regard to knee surgery, researchers proved that performing arthroscopic surgery on an arthritic knee, once a mainstay of surgical interventions for this condition, was no more effective than administering an anesthetic, making a skin incision, and performing a sham surgery. The outcomes in terms of pain and symptoms after either of these two procedures were virtually the same. The value of mammograms has also been seriously questioned, and it is unclear as to whether or not a mammogram has any influence on the number of women dying from breast cancer each year.

These observations are supported in the literature, which shows that many medical findings and treatment suggestions previously taken as the gold standard do not stand the test of time. John Ioannidis, known as a meta-researcher who has based his career on researching the validity of medical research findings, has shown time and time again in published studies that as many as 90 percent of the published medical information that doctors rely on is flawed.[13] Eighty percent of non-randomized studies (the most common type of studies) turn out to be wrong, and 25 percent of gold-standard randomized studies turn out to be wrong, as do 10 percent of platinum-standard large randomized trials. One of his papers[14] discussed his belief that researchers were frequently manipulating data analyses, choosing career-advancing findings rather than good science and using the peer-review process to suppress opposing views.[15] In perhaps one of the most ignominious examples of medical science undergoing a dramatic reversal in treatment approach, Dr. Egas Moniz received a Nobel prize in 1949 for his pioneering of the frontal lobotomy in 1936 to treat incurable mental illness.[16] Times do change, and sometimes, they change radically.

A *Wall Street Journal* article written by Ron Winslow entitled *Study Questions Evidence Behind Heart Therapies*[17] discussed a study that revealed that less than 11% of 2,700 recommendations commonly

---

[12] Family Practice News. (2003). 33(11), 1-2

[13] Freedman D., (2010). Lies, Damned Lies, and Medical Science. *The Atlantic*. Nov 2010 Issue.

[14] Ioannidis, J.P.A., (2005). Why Most Published Research Findings Are False. PLoS Med 2(8): e124. doi:10.1371/journal.pmed.0020124

[15] Freedman D., (2010). Lies, Damned Lies, and Medical Science. *The Atlantic.* Nov 2010 Issue.

[16] Csoka, A., (2015). Innovation in medicine: Ignaz the reviled and Egas the regaled. Med Health Care Philos. Springer Journal, Dec 4.

[17] *Wall Street Journal* |Feb 25th 2009

made by cardiologists were supported by scientific evidence. Furthermore, many of the dogmatic recommendations and guidelines created by cardiologists are formed by individuals who are connected in some financial way with the pharmaceutical companies.[18] Another study showed that 85 percent of individuals who had stents or angioplasties to treat their blocked coronary arteries did not need them. Furthermore, the group that did have the surgical procedures ended up much sicker than the individuals who treated their condition with drugs alone.[19] Thus, more critical evaluation of standards of practice was needed.

The original 1992 Evidence-Based Medicine Working Group set out specific criteria for assessing the strength of evidence that supports clinical decisions.[20] Has the diagnostic test been evaluated in a patient sample that included an appropriate spectrum of mild and severe disease, treated and untreated disease and individuals with different but commonly confused disorders?[21] Was there an independent, blind comparison with a gold standard of diagnosis?[22] Was the assignment of patients to treatments randomized?[23] Were all patients who entered the study accounted for at its conclusion?[24] Lastly, were explicit methods used to determine which articles to include at its conclusion?[25]

Evidence-based medicine utilizes specific steps to arrive at conclusions:

1) Ask the right question using an acronym PICO.[26] P=Patient or problem, I=Intervention, C=Comparison intervention, O=Outcome.
2) Acquire the best evidence by searching various databases, including but not limited to PubMed, Embase and Cochrane Library. Evidence-based medicine has various levels or grades for use in assessing the strength of studies.
3) Appraising the evidence: Is the study valid and relevant? What were the results of the study? Will the results help in treating the patient?
4) Apply the evidence. Once the evidence is obtained, it must be filtered through the patient's value systems and the level of the practitioner's core competencies. Shared decision making is essential once the risks and benefits have been explained.
5) Performance assessment. Whether this approach is helping and assisting the patient achieve his or her anticipated and expected health goals must be determined. This is done by assessing the four steps listed above.

There are four levels of evidence that are used when assessing the strength of studies via an EBM approach.

Level 1 – This is considered the top level of evidence, and it is derived from randomized, double-blind, placebo-controlled trials and/or meta analyses that combine the evidence from these trials. Meta-

[18] Rogers, S., (2009). Total Wellness. Aug, p. 1.
[19] Boden et al., (2007). New England Journal of Medicine. Optimal medical therapy with or without PCI for stable coronary artery disease. April 12, 356; 15:5003-16.
[20] Evidence-Based Medicine Working Group. (1992). Evidence-based medicine: A new approach to teaching the practice of medicine. JAMA, 268(2420), p. 2422.
[21] Department of Clinical Epidemiology and Biostatistics, McMaster University. (1981). How to read clinical journals, II: to learn about a diagnostic test. Can Med Assoc J. 124:703-710.
[22] Godfrey, K., (1985). Simple linear regression in medical research. N Engl J Med, 313, p. 1629-1636
[23] Department of Clinical Epidemiology and Biostatistics, McMaster University. (1981). How to read clinical journals, V: to distinguish useful from useless or even harmful therapy. Can Med Assoc J, 124, 1156-1162.
[24] Ibid.
[25] Ibid.
[26] University of North Carolina, Health Sciences Library. (2016). "Forming focused questions with PICO."

analyses are considered to be the most eligible for Level I status, but they too have come into some criticism as a means of evaluating critical evidence. Many studies that are combined in a meta-analysis are homogenous and lack sufficient outlying evidence.

Leve II – This evidence is not considered quite as reliable as that from Level 1. This evidence comes from controlled trials without randomization, cohort or case-control analytic studies and multiple-series studies.

Level III – This evidence is based on expert opinion from those specialized in one particular area under investigation. Most often, there are no control groups, and sample sizes are small. This approach can often lead to a large margin of error, unless statisticians compile the evidence from all expert opinions.

Level IV – This evidence is based on personal experience and is the least desirable source of evidence because it lacks statistical validity.

The original working group emphasised that it would require a specific teaching course and orientation, as taught at the McMaster University Medicine Residency Program, Department of Medicine, in order to critical appraise journal articles and arrive at the bottom line regarding the strength of evidence and how it may bear on the clinical problems in question. According to the original JAMA article, the residents "learn to present the methods and results in a succinct fashion, emphasizing only the key points. A wide-ranging discussion, including issues of underlying pathophysiology and related questions of diagnosis and management, follow the presentation of articles. They always substantiate decisions or acknowledge the limitations of the evidence and discuss the literature retrieval, the methodology of papers and the application to the individual patient."[27] This article emphasised that this "new paradigm will remain an academic mirage with little relation to the world of day-to-day clinical practice unless physicians-in-training are exposed to role models who practice evidence-based medicine". McMaster University recruited internists with training in clinical epidemiology and the "skills and commitment [needed] to practice evidence-based medicine." [28] This is a tall order for a busy clinically orientated profession, and even this article agrees that practicing in this way is fraught with complexity and difficulty. Furthermore, when first published, the authors asked whether advocating evidence-based medicine in the absence of definitive evidence of its superiority in terms of improving patient outcomes is an internal contradiction.[29]

One of the challenges facing a clinically trained and clinically based practitioner who does no in-house research and whose practise is full of competing demands is how to best evaluate the available evidence and make the best treatment decisions for patients who present every day with complex problems. The average physician spends far beyond 40 hours per week in the office, seeing patients, managing staffing issues and dealing with paperwork. The available paths to researching evidence-based literature and applying that information to complex patients with a multitude of issues are as follows:

1) Read journal article summaries at night with a critical eye on the quality of the research presented. Many doctors have a strictly clinical background, not a statistically orientated,

[27] Evidence-Based Medicine Working Group. (1992). Evidence-based medicine: A new approach to teaching the practice of medicine. JAMA, 268, p. 2420.
[28] Ibid.
[29] Ibid.

research-based background, and therefore, they may lack the knowledge to interpret research articles critically.

2) Read the opinion pieces or position papers of others who have read the original articles and commented on the quality of the research presented in association or interest group publications. Many of the position papers published by specific associations may not have the current best evidence and may not represent the best science available.
3) Attend conferences where the presenters, one assumes, are leading the field that the conference concerns, have done the necessary research and are presenting information based on Level I and Level II evidence-based research.
4) Listen to drug company reps who visit one's office with the details of the research concerning their products, which is presumably biased due to vested interests whether the product in question is a supplement or a drug.
5) Listen to patients' summaries of their internet searches and attempt to interpret their evidence into rational decision making.
6) Read up on what one's colleagues are discussing and/or referencing in online discussion groups.

From these beginnings, evidence-based medicine has had some major achievements. The Cochrane Collaboration was established to collate and summarise evidence from clinical trials, methodological and publication standards for primary and secondary research were established, national and international infrastructures were built to develop and update clinical practice guidelines, resources and courses were developed to teach critical appraisal and new knowledge bases for implementation and knowledge transition were built. [30]

However, since evidence-based medicine was first introduced and adopted, many cracks in the paradigm have appeared that warrant careful appraisal:

1) The coopting of clinical trials by invested drug manufacturing and medical device interests and the manipulation of data to suit endpoint outcomes has become subtler and harder to detect. These companies often set the research agenda, decide what is counted as a disease (i.e., sexual arousal disorder, which is treated with sildenafil), decide which tests and treatments will be compared and choose the efficacy outcome measures.[31] In addition, setting inclusion criteria to select those most likely to respond to treatment, manipulating the dosing of both intervention and control drugs and selectively publishing positive studies (while supressing negative outcomes) in leading peer-reviewed journals, with the assumption that their trials are unbiased, creates serious legitimacy issues regarding the conclusions reached. One review of industry-sponsored trials of antidepressants showed that 37 of 38 had positive findings but only 14 of 36 trials with negative findings were published.[32] Psychiatric prescription and drug trials are at the centre of many of these controversies.[33] Among the RTC studies in psychiatric journals, those that reported conflicts of interest were five times more likely

[30] Ibid.

[31] Cohen, D., (2013). "FDA official: Clinical trial system is broken." BMJ, p. 347.

[32] Turner, E., Matthews, A.M., Linardatos, E., Tell, R., Rosenthal, R. (2008). "Selective publication of antidepressant trials and its influence on apparent efficacy." N Eng J Med, 358, p. 252-60.

[33] Perlis, R.H. et al., (2005). "Industry sponsorship and financial conflict of interest in the reporting of clinical trials in psychiatry." Am J Psychiatry, 162(10), p.1957-60.

to report positive results. Large drug companies do not fund and are not interested in treatment interventions that do not support a pharmaceutical intervention.
Many studies that show the long-term benefits of compounded bioidentical hormone replacement therapy interventions do not make it to mainstream medical journals for these very reasons. A very contentious JAMA-published article, a retrospective observational study, indicated the negative effects of testosterone replacement therapy on cardiovascular disease, and this article changed the way that testosterone therapy was used in male andropause, despite the fact that many prior RCT studies had shown no such impact or favourable outcomes.[34]

2) The co-opting of policy makers (politicians) by the drug industry affects the introduction of certain evidence-based policies.[35]
3) A surplus of evidence results in unmanageable clinical guidelines.[36]
4) Large trials are designed to achieve marginal gains in a saturated therapeutic field and may tend to overestimate potential benefits. After many of the large early gains in research (the use of antiretroviral drugs in HIV and the use of triple antibiotic therapy in H. Pylori), new research has had to shift its focus to marginal gains in often overpowered trials that tend to underestimate harm (adverse effects undetected) and overestimate benefits (effects that are statistically but not clinically significant).[37] GlaxoSmithKline was fined $3 billion for multiple criminal and civil offences, such as false reporting, the unlawful promotion of medicines and failure to report safety data.[38]
5) The overemphasising of computerised decision support systems and defensive decision-making support technologies, as well as inexperience with complex presentations that do not comply with simple guidelines, may interfere with more experienced and nuanced clinical decision making on the part of an experienced practitioner who is somewhat accustomed to tolerating ambiguity and uncertainty in clinical decision making. [39]
6) Decision making may be driven by non-clinical staff who are incentivised by financial endpoints and not by nuanced quality of care for complex individual patients. “Patients may often feel tyrannized when their clinical management is inappropriately driven by algorithmic protocols, top-down directives and population targets.”[40]
7) Simple and/or complex algorithms do not fully apply to an aging population with complex presentations and comorbid conditions. Each person is genetically and biochemically unique (as is only too well-demonstrated in the CRS population), and although specific guidelines, as outlined by Dr. Shoemaker, must be followed to achieve success, there may still be many comorbid complexities that render the application of

---

[34] Vigen, R., MD, MSCS[1], et al., (2013). “Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels.” JAMA, 310(17), 1829-1836.

[35] Le Couteur, D.G., Doust, J., Creasey, H., Brayne, C. (2013). “Political drive to screen for pre-dementia: Not evidence based and ignores the harm of diagnosis.” BMJ, p. 347.

[36] Allen, D., Harkins, K. (2005). “Too much guidance?” The Lancet, 365, p. 1768.

[37] Greenhalgh, T., Howick, J., Maskrey, N. (2014). “Evidence-based medicine: A movement in crisis?” BJM. p. 348.

[38] Roehr, B., (2012). “GlaxoSmithKline is fined record $3billion in US.” BMJ. 345, p. e4568.

[39] Greenhalgh, T., Howick, J., Maskrey, N. (2014). “Evidence based medicine: A movement in crisis?” BMJ. p. 348.

[40] Ibid.

these same strict guidelines somewhat problematic, i.e., a patient with CIRS who has had a previous traumatic brain injury, complex early developmental trauma and a borderline personality disorder.

The authors of this critical 2014 BMJ paper, entitled "Evidence-based medicine: A movement in crisis?" suggest launching of a new campaign for what they termed "real evidence-based medicine". According to them, this is how to best describe what they mean by real evidence-based medicine and the remedying solution:

What is real evidence-based medicine, and how do we achieve it?

Real evidence-based medicine:

- *Makes the ethical care of the patient its top priority*
- *Demands individualised evidence in a format that clinicians and patients can understand*
- *Is characterised by expert judgment rather than mechanical rule following*
- *Shares decisions with patients through meaningful conversations*
- *Builds on a strong clinician-patient relationship and the human aspects of care*
- *Applies these principles at community level for evidence-based public health*

Actions to deliver real evidence based medicine:

- *Patients must demand better evidence that is better-presented, better-explained and applied in a more personalised way.*
- *Clinical training must go beyond searching and critical appraisal to hone expert judgment and shared decision-making skills.*
- *Producers of evidence summaries, clinical guidelines, and decision support tools must take account of who will use them and for what purposes and under what constraints they will be used.*
- *Publishers must demand that studies meet usability standards, as well as methodological ones.*
- *Policy makers must resist the instrumental generation and use of "evidence" by vested interests.*
- *Independent funders must increasingly shape the production, synthesis, and dissemination of high-quality clinical and public health evidence.*
- *The research agenda must become broader and more interdisciplinary, embracing the experience of illness, the psychology of evidence interpretation, the negotiation and sharing of evidence by clinicians and patients, and the prevention of harm from over-diagnosis.*

I believe some of these revised criteria have been met by Dr Shoemaker and his co-authors. Dr Shoemaker has published critiques of what has passed for evidence-based medicine guidelines in the management of mold illness prior to his ground-breaking work. The American College of Occupational and Environmental Medicine (ACOEM) and the American Academy of Asthma, Allergy and Immunology (AAAAI) published, in 2002 and 2006, respectively, guidelines reporting that mold exposure was not

capable of producing human illness. Much of the ACOEM "evidence" was based on opinion papers by defense consultants in litigation regarding water-damaged buildings (Bruce Kelman and Ronald Gots) and cited no human studies as reference material.[41] Dr. Shoemaker cited an article in the Wall Street Journal and an article by Craner that exposed the bias and concealed conflicts of interest of the ACOEM authors: "there is nothing evidence-based in either the ACOEM or AAAAI, as that process begins with the observation of affected patients." Dr Shoemaker is clearly using the criteria regarding the best way to practice evidence-based medicine in his criticism of their lack of fulfillment of these criteria in publishing these opinion papers.

I have relied almost exclusively on Dr Shoemaker and various co-authors of certain papers to understand the complexity of this multilayered condition. Dr Shoemaker is extremely insistent that the steps to be followed in the diagnosis and treatment of this condition must follow the guidelines set out by his own research, as well as clinical practice and treatment guidelines. It is obvious that he has followed an evidence-based approach in this undertaking. Dr Shoemaker began his original work with CIRS when he observed that patients with a mysterious disease seemed to improve when prescribed a lipid-lowering drug, cholestyramine. Based on that original observation, he explored the biology and pathophysiology of the disease processes in patients, using the best evidence available at the time, without the influence of financial interests. As he learned, he explored further hypothesises, published numerus studies, wrote books, collaborated with other researchers and lectured on the subject. He continues to utilise the best evidence-based practices in attempt to understand the genomics that underlie CIRS and how the use of VIP (and the rest of the CIRS protocol) influences the proteomic and Neuroquant findings of affected individuals.

The proof regarding whether an evidence-based approach is effective in managing CIRS patients is whether the patients involved in the study enjoy improved health as compared to controls. At present, there are no long-term randomized trials of the Shoemaker approach to treating CIRS. In other words, his research may not have fulfilled the Level I criteria regarding what type of research best characterises evidence-based medicine. However, his work has nonetheless systematically fulfilled most of the other criteria in that it is patient-centered and documents responses to care that are quantifiable and reproducible.

[41] Shoemaker, R. (2010). Surviving Mold: Life in the Era of Dangerous Buildings. Otter Bay Books: Baltimore, p. 310-311.