

# Science, Healing & Evidence

*How's a patient to figure this out? The case of CIRS*

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## Introduction

Fake news. Alternative facts. Conspiracy theories.

We live in a time where it has become more difficult for people to determine the truth. While this is particularly prominent in politics and the media it is also affects the area of medicine and science.

The concept of evidence based medicine (EBM) was a means to help get scientific research and evidence into clinical practice effectively – to help bring the truth to front line practice. This essay will discuss the use and benefits of EBM as well as its shortcomings and biases. It will comment on the research and diffusion of Chronic Inflammatory Response Syndrome into clinical practice as an example of the challenges involved in practically incorporating evidence into practice.

## The scientific method

The scientific method has been essential to human progress and advancing our understanding of the truth. The critical component of advancing science is being able to create hypotheses that can be systematically tested. The philosopher Karl Popper argued in the early 20<sup>th</sup> century that unless a hypothesis could be tested as false it could not be in the realm of science. The only way that we know a scientific hypothesis to be true is that it has withstood multiple assaults over a period of time to prove it false. There is no way to absolutely prove that something is true through the scientific method. In fact, science undergoes multiple paradigmatic shifts and revolutions as fundamental areas once thought to be true are ultimately proven false. Thomas Kuhn in his book, *The Structure of Scientific Revolutions* gives several examples of scientific revolutions, such as the Copernican Revolution.

*There are realms popularly thought of as being scientific, that aren't in the realm of science.* Karl Popper famously claimed that Freud's theories on psychoanalysis were not falsifiable as there was no easy way to put many of these theories to a test. How can you disprove that a patient doesn't have an Oedipal complex? Physics has a structure that readily lends itself to scientific testing. Sociology is more difficult to test. Many medical hypotheses are readily testable; however, the variability of human physiology and the potential of self-healing make it important that testing is rigorous.

*Advances in technology can expand what can be tested and held up to scientific scrutiny.* In the case of Freud, there has been the emergence of Big Data over the last 20 years such as people's anonymous searches. Datasets, such as one looking at people's typing errors to see if they have the classic "Freudian slip" have been used to disprove many of Freud's initial theories.<sup>1</sup> Another example is the expansion of

transcriptomics that allows clinicians and researchers to understand gene expression at the level of messenger and mitochondrial RNA. Researchers are now able to understand the impact of environmental exposure and treatment at the level of actual gene expression in patients. It is likely that many of our hypotheses on physiologic relationships will be proven false and new ones advanced.

## Healing vs. Science

Patients want the best care possible, consistent with their values and preferences. The healing physician takes scientific insights from the literature and looks to individualize care at the individual patient level with a moral duty to the patient.

All excellent physicians know that medicine ends up being a combination of science and art, because of the intrinsically variable nature of healing. Healing can happen due to medical treatment or it can often happen from individuals own self-healing mechanisms which can be variably activated. When it is tested in randomized clinical trials, this is often referred to as the “placebo effect.” In many trials of anti-depressants, the placebo effect can have an improvement of as much as 60-70%.

As practicing physicians, we want to maximize science and art and in most cases, there needs to be no tradeoff between the two.

Where does healing fall into the scientific method? It really depends on the perspective and role that role one assumes:

*As an individual caring clinician, I want to maximize healing wherever possible with a high margin of safety. I want to assure a strong patient-physician relationship; assure that the patient is following a healthy lifestyle and has a healing supportive environment wherever possible.*

*As a disciplined scrutinizer of the scientific literature, I want to make sure that the research has controlled for variability in healing using controls and randomization wherever possible.*

*As a values-driven professional who wants to see medicine improve in its ability to heal patients, I am interested in new technological advances that help to create more testable hypotheses on the nature of healing. The human body is an extraordinarily complex adaptive system. The emergence of precision medicine – genomics, proteomics, transcriptomics, and metabolomics – promise to help tailor our therapy. However, we should not expect that science will shine a light on all aspects of healing. To the degree that patients can control healing mechanisms, there is likely to be tremendous variability in healing. I suspect there will always be aspects of healing that fall outside of the scientific method.*

We can see these conflicts at play within the emergence of integrative medicine as a new practice of medicine. Integrative medicine has looked to integrate multiple schools of healing and incorporate holistic and Eastern philosophies of healing. Practitioners want to appropriately optimize the healing process; many times, they have been able to create health care delivery microsystems that are better at optimizing healing factors than conventional medicine.

However, it has been difficult to prove many integrative medicine concepts through traditional scientific means. Sometimes this is because the science is weak and does not fall into a coherent framework as in

the case of homeopathy. Other times this can be because of the desire to individualize care beyond current capabilities for science to disprove the individualization strategy. EBM gives a good framework for operationalizing interventions – the evaluation of benefits versus risks. If there is a treatment that is not substantiated by the data it needs to have a higher margin of safety, there needs to be few good options available and it needs to be fully aligned with patient preferences.

The danger in incorporating new philosophies into medicine is when there becomes a self-referential cycle of attacking the scientific basis of medicine using pseudoscience methods. This can be seen in the case of vaccines. The public is predisposed to these attacks, because ongoing exposes on the fallibility of formerly trusted institutions has created an atmosphere of mistrust.<sup>2</sup> The noted surgeon and best-selling author Dr. Atul Gawande identified the pseudoscientific issue with more precision in a 2016 graduation address at Cal Tech<sup>3</sup>:

*Science's defenders have identified five hallmark moves of pseudoscientists. They argue that the scientific consensus emerges from a conspiracy to suppress dissenting views. They produce fake experts, who have views contrary to established knowledge but do not actually have a credible scientific track record. They cherry-pick the data and papers that challenge the dominant view as a means of discrediting an entire field. They deploy false analogies and other logical fallacies.*

*And they set impossible expectations of research: when scientists produce one level of certainty, the pseudoscientists insist they achieve another.*

*It's not that some of these approaches never provide valid arguments. Sometimes an analogy is useful, or higher levels of certainty are required. But when you see several or all of these tactics deployed, you know that you're not dealing with a scientific claim anymore.*

*Pseudoscience is the form of science without the substance.*

## Evidence based medicine

Evidence based medicine was a movement in the late 1980's to help clinicians codify science and evidence into clinical practice. David Sackett one of the founders of EBM wrote "Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients." It is based on the premise that the guidelines for the most effective clinical treatment of any condition should be based on the best scientific research possible instead of relying *only* on clinical judgment and past experience.

There are 3 EBM principles that are used to make decisions about the care of individual patients. Most of the emphasis and controversy on EBM has been on the research principle but the 2<sup>nd</sup> and 3<sup>rd</sup> principles have been critical to advancing good patient care.

1. Evaluation of valid current research
2. Incorporating patient values and expectations into decision making
3. Evaluating likely treatment benefits versus the risks

Evaluation of valid current research has been compounded by the exponential increase in the amount of research over the past few decades. EBM proponents demanded that clinical studies be designed properly. They rated the quality of primary evidence in a pyramid (from top to bottom)

- *Level 1 evidence* comes from randomized, double-blind, placebo controlled trials and or meta-analyses that combine the evidence from these trials.
- *Level 2 evidence* comes from controlled trials without randomization, prospective cohort or retrospective case-control studies and multiple time-series studies
- *Level 3 evidence* comes from expert opinion and case series.
- *Level 4 evidence* comes from personal experience.

EBM proponents also developed methods of meta-analysis where different trials and studies on a topic could be analyzed as an aggregate.

The promise of evidence based medicine was to take a more critical look at research and evidence in translating this to medical decisions. And this has succeeded in part.

Insurance companies and international health systems jumped on the notion of EBM over that last 20 years. Decision makers in these institutions were driven by their need to make defensible decisions *today* about what should be covered by insurance or excluded as a nature of health policy. EBM was a shiny new tool that would give cover to these decisions. They could use EBM methods to develop clinical guidelines that could then act as a basis for medical policy determinations of the coverage of benefits and provide methods for insurers to judge quality of care on a large scale.

What was unanticipated was the downsides of using EBM as there are a number of important biases that aren't accounted for by the EBM process. The practicing physician, policy maker and decision maker all need to understand these biases. Dr. John Ioannidis in a highly influential paper in PLOS<sup>4</sup> showed how biases can affect the scientific literature (not just medicine). He outlines 6 corollaries that collectively reduce the level of positive predictive value in any particular new study:

- The smaller the studies conducted in a scientific field, the less likely the research findings are to be true.
- The smaller the effect sizes in a scientific field, the less likely the research findings are to be true.
- The greater the number and the lesser the selection of tested relationships in a scientific field, the less likely the research findings are to be true.
- The greater the flexibility in designs, definitions, outcomes, and analytical modes in a scientific field, the less likely the research findings are to be true.
- The hotter a scientific field (with more scientific teams involved), the less likely the research findings are to be true.
- The greater the financial and other interests and prejudices in a scientific field, the less likely the research findings are to be true

The last corollary encompasses several critical biases that deserve expansion. *Institutional prejudices* can be highly subtle and can be displayed in multiple ways – whether the research study is submitted (e.g., pharmaceutical companies not submitting failed trials) or whether peer reviewers demonstrate bias based on the relative fame of the author or prior belief in the hypothesis. *Funding bias* is an additional

point. The resources to properly do a randomized controlled clinical trial are significant. A 2010 JAMA study quantified the US biomedical research industry at \$100 billion annually; pharmaceutical, biotech and medical device industry contributes 58%; the government contributes 33% with foundation, advocacy organizations and individual donors responsible for the remainder.<sup>5</sup> Because of the sources of funds, most of the research will be to support new for-profit pharmaceutical and device interventions. Government funding should be geared to support research outside of the for-profit system but can have its' own biases around fame and existing players. *Publication bias* is another challenge. There is a strong bias by journals to only publish positive results and omit negative results. Only half of the studies posted in ClinicalTrials.Gov are published.

A critical bias in EBM that individual physicians need to consider is the promotion of *population health over individual care*. The appeal of EBM to institutions is that it allows predictability and management of diseases at the population level. But the physician needs to take general findings and individualize it to the care of the individual patient. Professor Sandra Tannenbaum asserts: "EBM has remained mostly silent on the inferential leap from aggregate to individual that is required for actual clinical care."<sup>6</sup> Many of the studies involved in the evidence remove complex patients from the population which then makes it more difficult to individualize care. Some have gone so far as to critique EBM for applying a *utilitarian* framework that is contradictory to the physician's duty to the individual patient at hand.

### The case of CIRS

The case of CIRS is an example of the challenges in how medicine incorporates scientific advances using an EBM framework. The institutions that are the gatekeepers of EBM – the Cochrane Collaborative, UpToDate, specialty society guidelines – are all currently silent on the topic of Chronic Inflammatory Response Syndrome, despite the considerable number of scientific papers written on the topic.

We know that it usually takes 20 years from the time that many advances in medicine are shown to be true to the time it is adopted. The treatment of peptic ulcer disease for H pylori is a classic example. Usually the exceptions to this rule are ones in which the new intervention makes more money for the clinicians (e.g., cardiac angioplasty) or interventions that deliver financial returns to institutions with a significant financial capital on their balance sheets such as the medical device, pharmaceutical, biotechnology companies.

By the lens of the scientific method, the advances in CIRS have happened at a rapid rate and incorporated the latest in medical technology

- There was the classic scientific chance discovery – rapid clinical improvement in patients exposed to biotoxins from Pfisteria that responded to treatment with cholestyramine. Insights from this chance discovery were applied to a broader set of patients in the true spirit of science.
- The underlying biological mechanism were systematically developed. Many of these mechanisms cut across multiple systems and ended up involving mechanisms not commonly tested in clinical practice, which worked against rapid adoption.
- Randomized clinical trials occurred for the early part of the treatment protocols, i.e., cholestyramine
- Testing of the individual biological mechanisms have been held to high standards of causality in medical science, for example:
  - Re-exposure protocols show that the CIRS response can reoccur in a predictable manner

- Transcriptomics that show how treatment of CIRS can turn off gene activation
- NeuroQuant data that shows that atrophic areas of brain can regrow tissue when the underlying mechanism is treated

Yet with 20 years of data, CIRS in 2017 today still exists outside of the “conventional medicine grid.”

Why is that? I believe there are a number factors at play:

- *Thinking that cuts across a number of specialties* – Science and clinical practice favors the specialist. Understanding CIRS requires learning new areas of biomedical research cutting across different specialty areas and getting into environmental areas as well. There’s not just one new therapy to learn. Multi-disciplinary thinking also makes it more difficult to get NIH grants.
- *Paradigmatic change in thinking* – the pathways that exist in CIRS are built from basic science but do not readily build from accepted conventional wisdom. Many of the lab tests involved are not usually run by clinicians.
- *Bias towards randomized controlled clinical trials within EBM and needed advances in research design to test multifactorial protocols.* There has not been a full randomized controlled clinical trial of the complete Shoemaker protocol. Testing a multi-factorial protocol requires significantly more resources to design a clinical trial than testing an individual drug. Dr. Dale Bredesen faces similar challenges in structuring a randomized clinical trial of his Bredesen protocol for Alzheimer’s. Accomplishing this will likely require a 3<sup>rd</sup> party with vested financial interest.
- *Insufficient capital for randomized clinical trials and resources for stakeholder marketing* – To date, there has not been a 3<sup>rd</sup> party with vested financial interest that could deploy significant marketing resources to influence a variety of stakeholders (e.g., specialty societies, research institutions, individual physicians). A 3<sup>rd</sup> party will probably be necessary to fund the considerable capital for a full randomized clinical trial.
- *Controversy and backlash from existing institutions* – The issues of water damaged buildings in the courts gave rise to institutions that had vested interest in downplaying CIRS as a real entity.

Despite these challenges, progress in the care of patients with CIRS moves forward at a considerable rate. These challenges have been with us for some time -- Max Planck, the notable physicist who originated quantum theory stated in his autobiography in the early twentieth century:

*“A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it. Science advances one funeral at a time.”*

## Footnotes

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<sup>1</sup> Stephens-Davidowitz. *Everybody Lies. Big Data, New Data and What the Internet can tell us about who we really are.* 2017. Harper Collins.

<sup>2</sup> Callahan C. *The Cheating Culture: Why More Americans are Doing Wrong to Get Ahead.* 2003.

<sup>3</sup> Gawande, A. *The Mistrust of Science.* *The New Yorker* June 10 2016.

<sup>4</sup> Ioannidis JP. *Why Most Published Research Findings Are False* *PLOS* August 30, 2005.

<sup>5</sup> Dorsey ER, et al. *Funding of US Biomedical Research 2003-08.* *JAMA.* 2010;303(2):137-143.  
doi:10.1001/jama.2009.1987

<sup>6</sup> Tanenbaum S. *Particularism in healthcare: challenging the authority of the aggregate.* *Journal of Evaluations in Clinical Practice* 20: 934-41