



History and Development of Evidence-based Medicine

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Abstract. This article illustrates the timeline of the development of evidence-based medicine (EBM). The term “evidence-based medicine” is relatively new. In fact, as far as we can tell, investigators from McMaster’s University began using the term during the 1990s. EBM was defined as “a systemic approach to analyze published research as the basis of clinical decision making.” Then in 1996, the term was more formally defined by Sacket et al., who stated that EBM was “the conscientious and judicious use of current best evidence from clinical care research in the management of individual patients.” Ancient era EBM consists of ancient historical or anecdotal accounts of what may be loosely termed EBM. This was followed by the development of the renaissance era of EBM, which began roughly during the seventeenth century. During this era personal journals were kept and textbooks began to become more prominent. This was followed by the 1900s, during an era we term the transitional era of EBM (1900–1970s). Knowledge during this era could be shared more easily in textbooks and eventually peer-reviewed journals. Finally, during the 1970s we enter the modern era of EBM. Technology has had a large role in the advancement of EBM. Computers and database software have allowed compilation of large amounts of data. The Index Medicus has become a medical dinosaur of the past that students of today likely do not recognize. The Internet has also allowed incredible access to masses of data and information. However, we must be careful with an overabundance of “unfiltered” data. As history, as clearly shown us, evidence and data do not immediately translate into evidence based practice.

This article outlines the timeline of the development of evidence based medicine (EBM). It is in no way meant to be a complete account of its development. We start with some of the first accounts of EBM and proceed to the present time and what we now define as modern era EBM. Thus, we should start with a definition. The term “evidence-based medicine” is a relatively new one. As far as we can tell, investigators from McMaster’s University began using the term during the 1990s [1–3]. EBM was defined as “a systemic approach to analyze published research as the basis of clinical decision making.” Then, in 1996, the term was more formally defined by Sacket et al., who stated that EBM was “the conscientious and judicious use of current best evidence from clinical care research in the management of individual patients” [4].

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One of the first references regarding the practice of EMB did not appear until 1993 in the *Journal of the American Medical Association* [5, 6]. Since then, the concept of EBM took a few years to take hold but now has been accepted globally. Evaluating the keywords “evidence-based medicine” in MEDLINE shows a linear increase in its use over the past decade (Fig. 1). The term EBM may be new and is being actively taught in medical schools, but the concept has been around for a long time. Granted, with the advent of the computer, large databases, and the Internet; the methods and efficacy of the practice of EBM has changed. However, in reviewing medical history there are many examples that illustrate the development of EMB, if one remembers the definition as “the conscientious and judicious use of current best evidence from clinical care research in the management of individual patients.”

Time Periods of EBM

No one would deny that our teaching methods have changed over the past several centuries. We have moved through authoritative styles of teaching, apprenticeships, and now to teaching EBM. Surgery has retained all aspects of the varied teaching methods; however, as time has passed dogma has become increasingly questioned. By questioning standard teaching, students of medicine eventually began to look for other treatments and explanations. In other words, they were looking for rationale and evidence.

We have loosely traced a timeline in the development of EBM. The initial period we termed ancient era EBM. Ancient era EBM consists of ancient historical or anecdotal accounts of what may be loosely termed EBM. Teaching during this time was mainly authoritative and passed on with stories. This was followed by the development of the renaissance era of EBM, which began roughly during the seventeenth century. During this era personal journals were kept, and textbooks began to become more prominent. This was followed by the 1900s in an era we term the transitional era of EBM (1900–1970s). Knowledge during this era could be shared more easily in textbooks and eventually peer-reviewed journals. Finally, during the 1970’s we entered the modern era of EBM. During this era we have had an informatics explosion with online journals and large databases. As history brings us closer to the present day, one theme emerges. The presence of evidence does

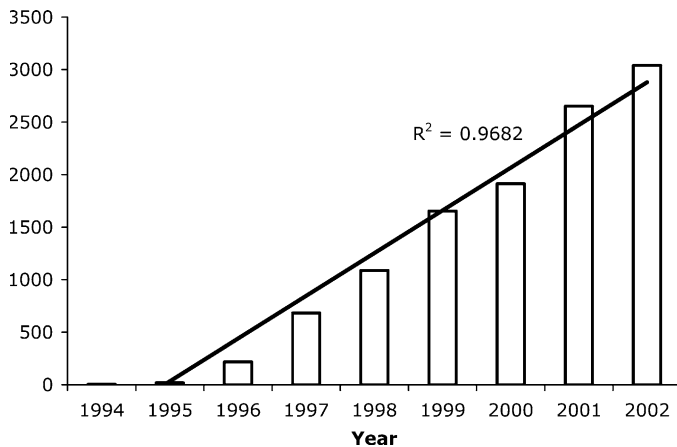


Fig. 1. Number of papers on MEDLINE per year with keywords “evidence-based medicine” demonstrates a liner increase with time ($r = 0.98$).

not immediately translate into the practice of EBM. However, we have seemed to decrease the lag time between discovery and application.

Ancient Era EBM

The first reference we found had little to do with surgery. In fact, it is a Biblical reference. Regardless of religious belief, this story or anecdote does give a primitive example of a controlled study [7].

Then Daniel said to the guard whom the master of the eunuchs had put in charge of Hananiah, Mishael and Azariah and himself. “Submit us to this test for ten days. Give us only vegetables to eat and water to drink; then compare our looks with those of the young men who have lived on the food assigned by the king and be guided in your treatment of us by what you see.” The guard listened to what they said and tested them for ten days. At the end of ten days they looked healthier and were better nourished than all the young men who had lived on the food assigned them by the king.

A second example of ancient EBM comes from 1061 and the Song Dynasty. Ben Cao Tu Jing was quoted as saying, “In order to evaluate the efficacy of ginseng, find two people and let one eat ginseng and run, the other run without ginseng. The one that did not eat ginseng will develop shortness of breath sooner” [8].

These two examples are simple yet still have some elements of modern era EBM. There are likely many more anecdotes and historical accounts of ancient EBM. To review them would likely take a career of a historian. We just wanted to introduce the concept that some of the principles of EBM have been around for many years.

Renaissance Era EBM

The renaissance era began during seventeenth century. We found two main themes that show examples of EBM and its development. Blood-letting as a treatment modality and the scurvy are two themes that reverberate throughout the history of this period.

Bloodletting dates back to 1000 years BC to the Egyptians. Eventually this traditional treatment spread to the Greeks and Romans. The popularity of bloodletting continued throughout the

Middle Ages and eventually reached its zenith during the beginning of the nineteenth century. It was not until the end of the nineteenth century that this practice died. To modern-day physicians it may be difficult to understand why this therapeutic tool survived so long. The story and its role in practice is a great introduction to EBM. The eventual disappearance of bloodletting demonstrates the evolution of EBM and its eventual practice.

Let us begin with the contemporary theory of disease at the time of bloodletting. Primitive man is said to have looked on disease as a curse cast on him by an evil spirit; his treatment consisted of driving out the demon that possessed him. The premise was that the evil spirit of disease was contained within the skull and could be drawn out. In much the same way as trepanation allowed demons to escape from the head, bloodletting was supposed to facilitate the release of evil spirits from elsewhere in the body. Later use of bloodletting for diseases such as hypertension, apoplexy, dropsy, and, nervous disorders may have had more of a physiologic explanation. This ancient practice was not formally questioned until the seventeenth century.

One of the first accounts of challenging the efficacy of the treatment of bleeding was by van Helmont [9]. He is quoted as saying; “Let us take out of the Hospitals, out of the Camps, or from elsewhere, 200, or 500 poor People, that have fevers or Pleuritis. Let us divide them in Halfes, let us cast lots, that one halfe of them may fall to my share, and the others to yours; I will cure them without blood-letting and sensible evacuation; but you do, as ye know ... we shall see how many Funerals both of us shall have...” We are not sure if this “study” was performed, but the questioning of the practice of bloodletting was clearly articulated in this passage.

In the next century a surgeon, John Clark, with the East India Company challenged the ideologies of the Army’s Surgeon-in-Chief, Sir John Pringle, who recommended copious bleeding for fevers. It is suggested that Clark began to change the method of practice after noting that three of his own patients become unconscious after such treatment. He changed his treatment of such maladies to Peruvian (cinchona) bark. More importantly he reported his case, including both successful and fatal cases [10]. Thus he began to look for evidence on which to base his decisions. Later in life Clark went on to add much more to medicine and in particular to the development of EBM.

At the beginning of the next centuries others went on to evaluate the efficacy of bloodletting. In 1816, a military surgeon name Alexander Lesassier Hamilton reported an experiment in his M.D. thesis. This took place in 1809, in Portugal, and it involved 366 sick soldiers. In the experiment Hamilton and two other army surgeons used rotation to generate comparable groups. The crucial paragraph [11] reads:

It had been so arranged, that this number was admitted, alternately, in such a manner that each of us had one third of the whole. The sick were indiscriminately received, and were attended as nearly as possible with the same care and accommodated with the same comforts. One third of the whole were soldiers of the 61st Regiment, the remainder of my own (the 42nd) Regiment. Neither Mr Anderson nor I ever once employed the lancet. He lost two, I four cases; whilst out of the other third [treated with bloodletting by the third surgeon] thirty five patients died.

However, there is controversy over this trial and if it truly took place. Even if this study is controversial, it still illustrates the development of the process of EBM. Yet, even if evidence is

generated, it does not translate immediately to evidence based practice. Bloodletting is a great example of this. Despite some challenges and data against the practice of bloodletting, pamphlets recommending bloodletting were still being written by serving officers in 1813 [11].

French physicians were also evaluating bloodletting in a more scientific approach versus a dogmatic approach. Most prominent among these was Pierre Charles-Alexandre Louis (1787–1872), known for his application of “la méthode numérique” [the numerical method] to assess the effects of bloodletting [12]. His findings were reported in greatest detail in his 1835 monograph “Recherches sur les effets de la saignée” [Research on the effects of bloodletting], which was published in Boston the following year [13]. There was no prospective element in Louis’ “method,” however. It consisted of retrospective analyses of case series derived from both his own practice and hospital records, and it used simple tabular presentations and calculation of average mortality rates.

Not long after, a young contemporary of Louis, Jules Gavarret, took a step closer to present-day concepts of the proper use of statistical methods for assessing the results of treatment. Gavarret was born in 1809 and served for a few years as an artillery lieutenant in the French Army, but he resigned his commission in 1833 to begin scientific studies with Gabriel Andral (1797–1876), an eminent Parisian physician who pioneered studies of blood chemistry. Gavarret published his findings in 1840 in his *Principes Générate de Statistique Médicate* [General Principles of Medical Statistics] [14], in which he also drew attention to the problems likely to arise from attempts to compare specific treatments in two groups of patients who might differ in respect to factors such as economic and social circumstances, diagnostic criteria, and other features of treatment.

Scurvy

Scurvy is a condition that has been described for at least 500 years. It produces characteristic perifollicular hemorrhages and gingival changes as well as hematologic, joint, and cardiac complications. Scurvy is now known to be caused by a prolonged deficiency of vitamin C intake that results in defective collagen synthesis and defective folic acid and iron utilization.

The discovery, prevention, and treatment of scurvy contribute another story in the development of renaissance era EBM. A key to this era is the reiteration that evidence is neither easily nor rapidly translated into practice. Scurvy was a serious problem when fresh fruits and vegetables were not available during the winter in many parts of the world. It was especially common among sailors in the days when only nonperishable foods could be stocked aboard ship. More than half the crew of Vasco da Gama died from scurvy on his first trip (1497–1499) around the Cape of Hope, although at the time the etiology of the deaths was unknown.

It was not until nearly two centuries later, in the 1600s, that John Woodall described his experience with scurvy and stated, “the Lemmons, Limes, Tamarinds, Oranges, and other choice of good helps in the Indies...do farre exceed any that can be carried tither from England” [15]. However, this was overlooked for more than another century. It was not until the mid-1700s when Sir James Lind shed more light on the subject of scurvy. In 1753 he published *A Treatise of the Scurvy* [16]. However, it was not until

40 years later that Sir Gilbert Blane convinced the admiralty of the British Navy to approve a preventive dietary regimen for sailors. In Lind’s writings he described the following.

On the 20th May, 1747, I took twelve patients in the scurvy on board the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet in common to all.

Two of these were ordered each a quart of cyder a day. Two others took twenty-five gutts of elixir vitriol three times a day upon an empty stomach, using a gargle strongly acidulated with it for their mouths. Two others took two spoonfuls of vinegar three times a day upon an empty stomach, having their gruels and their other food well acidulated with it, as also the gargle for the mouth. Two of the worst patients, with the tendons in the ham rigid (a symptom none the rest had) were put under a course of sea-water. Of this they drank half a pint every day and sometimes more or less as it operated by way of gentle physic. Two others had each two oranges and one lemon given them every day. The two remaining patients took the bigness of a nutmeg three times a day, of an electuary recommended by an hospital surgeon made of garlic, mustard seed, rad. raphan, balsam of Peru and gum myrrh, using for common drink barley-water well acidulated with tamarinds, ... with the addition of cremor tartar, they were gently purged three or four times during the course.

As I shall have occasion elsewhere to take notice of the effects of other medicines in this disease, I shall here only observe that the result of all my experiments was that oranges and lemons were the most effectual remedies for this distemper at sea.

In summary, the history of scurvy in the British Navy during the second half of the eighteenth century shows how comparative trials in controlled conditions of time and environment were well described by Lind. However, despite the data, translation of evidence into practice was imperfect and practiced on a small scale. Part of this delay in changing practice was that the pathophysiological explanation of scurvy remained speculative. The record-keeping of accurate observations and simple numerical records from individual ships and whole fleets in wartime became more important. Eventually, both the clinical features of scurvy and the effects of preventive and therapeutic strategies became better assessed and understood. This led ultimately to a change of professional and political opinion in favor of lemon juice among the authorities directing the naval service and thus to the conquest of scurvy.

Surgical Technique During the Renaissance Era of EBM

As one reviews history, there are examples of the development of EBM for surgical techniques in this pioneer era. An early example of observation in the treatment of burns comes from the works of the famous surgeon Ambroise Paré, who wrote the following about a patient who was burned after falling into a caldron of oil [17].

Treatment with standard medical practice vs. that recommended by a “country woman.” The country woman stated that ...I should lay two raw Onions beaten with a little Salt; for so that should hinder the breaking out of blisters or pustules... the next day found those places of his body whereto the Onions lay, to be free from blisters, but the other parts which they had not touched, to be all blistered.

Table 1. Results of Cheselden's lithotomy operations.

Age (years)	Operated on (No.)	Died (No.)
< 10	105	3
11–20	62	4
21–30	12	3
31–40	10	2
41–50	10	2
51–60	7	4
61–70	5	1
71–80	2	1
Total	213	20

Another example of the principles of EBM being employed are demonstrated by William Cheselden, who is closely linked with the use of lithotomy, an operation to remove bladder stones. When Cheselden was trying to make his way in London in the 1710s, he had used suprapubic lithotomy. Although he did eight successful operations out of nine between May and October 1722, his enthusiasm for the suprapubic operation soon faded. Cheselden continued to alter his technique during the early to mid-1700s. Cheselden's fame spread quickly. In fact, it reached Paris even before he had had time to publish his results in 1730. Cheselden went to considerable trouble to assure his readers of the truthfulness of his results. He gave a list of all 46 patients operated on between March 1727 and July 1730, with their ages and dates of operation. Cheselden continued to keep accurate records of his suprapubic practice [18]. He wrote:

What success I have had in my private practice I have kept no account of, because I had no intention to publish it, that not being sufficiently witnessed. Publicly in St. Thomas's Hospital I have cut two hundred and thirteen; of the first fifty, only three died; of the second fifty, three; of the third fifty, eight; and of the last sixty-three, six. "If the trend in mortality rates had increased somewhat, Cheselden believed that this was because in the later series the operation being sought by "even the most aged and most miserable cases expected to be saved by it."

Cheselden's reports demonstrate an early recognition of the need, when trying to make fair assessments of medical treatments, to take into account the age distribution of patients receiving treatment when age may influence treatment outcome. Table 1 [18] demonstrates Cheselden's results. The importance of Cheselden's analysis was appreciated long after his work. His crude (overall) mortality figures after lithotomy continued to be presented as a measure of the success of the operation well into the nineteenth century.

The development of amputation techniques is yet another example of EBM in practice. Edward Alanson acquired a reputation for having induced a "revolution" in amputation technique: By combining the flap technique with the immediate postoperative union of the skin edges by apposition, he hoped to achieve healing by first intention. Feeling responsible to the public when changing the technique of amputation—an operation "terrible to bear, horrid to see, and [which] must leave the person on whom it has been performed, in a mutilated imperfect state" [19]. Alanson substantiated the superiority and presented the results of his analyses using this "historical control group." He also referred to some of the pitfalls in the *Practical Observations on Amputations* (1779) [20].

Transitional Era of EBM

The transitional era began during the late nineteenth century and lasted to roughly the 1970s. A key figure during this era was Ernest Amory Codman (1869-1940). In the literature he has been called both the "Pioneer of evidence-based medicine" and the "improper Bostonian" [21, 22]. Codman developed a revolutionary but simple concept that he called "the end result idea" [23]. His practice was to develop 5 × 8 inch cards for every operation, and he detailed the preoperative and postoperative care. The card was brought up a year later and the patient reexamined and evaluated for results relative to therapy. He developed a classification of errors for adverse outcomes. He reported his results honestly and made them widely available to all. Codman thought the end-result idea could be used to compare hospitals and surgeons. However, the idea was controversial and clearly shook the standard at the time of measuring a surgeon's status. Status was measured by seniority, not by outcomes. He also made some important contributions relative to the American College of Surgeons. In 1910, after attending the Royal College in Britain, he observed that an American College would be a good place to introduce his end results idea and to standardize hospitals. The American College of Surgeons was established 3 years later, in 1913. Prompted by his stimulation, the American College of Surgeons developed a committee called the Standardization of Hospital during the late 1920s that ultimately became the Joint Commission for the Accreditation of Hospitals in 1957. Codman's efforts culminated in 1914 in his address to a large audience of medical leaders in Philadelphia titled "The product of a hospital." He stated that hospitals were responsible for the care given by their staff and thus should carefully note the results of each surgeon. Furthermore, he believed that these results should be available to the public. Unfortunately, his talk was novel and unprecedented, and it was likely perceived at the time to be blunt, shocking, and brash. He eventually had to leave the Massachusetts General Hospital because of a difference in opinions and established his own "end result" hospital. Many of Codman's ideals are key to the success of modern era evidence based medicine. As an example, Codman also went on to begin the registry of bone sarcoma, which was America's first tumor registry. Many registries, including trauma and tumor registries, now exist based on some of Codman's initial concepts. These registries are a key element in modern era EBM, as they allow outcomes research and establishment of benchmarks.

Another concept that emerged during this Transitional Era of EBM was the utilization of randomized clinical trials (RCTs). Granted there were accounts of this in previous eras but it was in this era of EBM that the use of RCTs truly developed. The use of randomization in the Medical Research Council's clinical trial of streptomycin in pulmonary tuberculosis during the 1940s likely attracted the most notoriety [24]. However, earlier a trial of treatment of tuberculosis was described by randomizing two groups (treatment with sanocrysin vs. control) by a flip of a coin [25]. This study, published in 1931, also described the patients and physicians being blinded. G. W. Theobald, an obstetrician in London who studied the effects of calcium and vitamin A and D on the incidence of pregnancy toxemia, performed another well documented clinical trial. This study was published in 1937 [26]. Following this study by Theobald, the People's League of Health in London did further studies evaluating dietary supplements

Table 2. Grading systems of evidence and recommendations according to three organizations.

Grade	IDSA		SSCM		EAST	
	Criterion	Grade	Criteria	Grade	Criteria	
Strength of recommendation A	Good evidence to support a recommendation for use	A	Supported by at least two level I investigations	Level 1	Convincingly justifiable based on the available scientific information alone. Usually based on class I data, however, strong class II evidence may form the basis for a level I recommendation, especially if the issue does not lend itself to testing in a randomized format	
	Moderate evidence to support a recommendation for use	B	Supported by only one level I investigation	Level 2	The recommendation is reasonably justifiable by available scientific evidence and strongly supported by expert opinion. Usually supported by class II or a preponderance of class III evidence	
	Poor evidence to support a recommendation for use	C	Supported by level II investigations only	Level 3	Supported by available data but adequate scientific evidence is lacking. Generally supported by class III data	
	Moderate evidence to support a recommendation against use	D	Supported by at least one level III investigation			
	Good evidence to support a recommendation against use	E	Supported by level IV or level V investigations only			
Quality/grading of evidence I	Evidence from at least one randomised, controlled trial	Level I	Large, randomized trials with clear-cut results; low risk of α and/or β error	Class I	Prospective randomized controlled trials	
	Evidence from at least one well designed clinical trial without randomization	Level II	Small, randomized trials with uncertain results; moderate to high risk of α and/or β error	Class II	Clinical studies in which the data were collected prospectively, and retrospective analyses based on clearly reliable data	
	Evidence from opinion of respected authors, based on clinical experience, descriptive studies, or reports of expert committees	Level III	Nonrandomized, contemporaneous controls	Class III	Studies base on retrospectively collected data	
II		Level IV	Nonrandomized, historical controls and expert opinion			
		Level V	Case series, uncontrolled studies, expert opinion			

IDSA: Infectious Disease Society of America; SSCM: Society of Critical Care Medicine; EAST: Eastern Association for the Surgery of Trauma.

using large numbers of pregnant females. They published their results over the next several years in what is likely the largest studies of the kind [27, 28].

Thus, the transitional era of EBM heralds the use of RCTs and leads us to today, and the modern era of EBM. In fact, one of the founders of EBM Archie Cochrane, was also an author of a paper utilizing randomization in titled "... my first, worst, and most successful clinical trial [29]. In this paper he described curing a disease of prisoners of war by randomizing half of them to receive yeast for the treatment of beri-beri. Although he demonstrated improvement in his treatment group, he later learned that his diagnosis was wrong and his methodology flawed. Fortunately, he continued to work and eventually led us to the modern Era of EBM.

Modern Era EBM

Modern era EBM begins during the late twentieth century. Two main figures have been given credit for establishing what we now know as EBM. They are, as previously mentioned, Archie Cochrane from the United Kingdom and David Sackett from Canada. Archie Cochrane's published his classic text in 1972: "Effectiveness and efficiency: random reflections on health services." This text has had a profound influence on the practice of medicine and on the evaluation of medical interventions. He was the first to set out clearly the vital importance of RCTs for assessing the effectiveness of treatments. His work led directly to the setting-up of the Cochrane Center, which later became the Cochrane Collaboration. The Cochrane Collaboration is a worldwide endeavor dedicated to tracking down, evaluating, and synthesizing RCTs in all areas of medicine. The Cochrane Collaboration is an international nonprofit, independent organization dedicated to making up-to-date, accurate information about the effects of health care readily available worldwide. It produces and disseminates systematic reviews of health care interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions. The Cochrane Collaboration was founded in 1993 and named for the British epidemiologist. A major product of the Collaboration is the Cochrane Database of Systematic Reviews, which is published quarterly as part of The Cochrane Library. Those who prepare the reviews are mostly health care professionals who volunteer to work in one of the many Collaborative Review Groups, with editorial teams overseeing the preparation and maintenance of the reviews,

David Sackett is credited with defining the term EBM. In 1967 he moved to McMaster University in Canada to help start a new medical school and a new way of training physicians: no courses and no lectures, but working with and for patients from day 1. In 1994 Oxford University created a chairmanship position, enabling him to found the world's first center for evidence based medicine.

Many other organizations have tried to incorporate the fundamentals of EBM into their practice/management guidelines. One of those is the Eastern Association for the Surgery of Trauma (EAST). EAST has developed practice/management guidelines for the treatment of trauma patients based on the best evidence available. These guidelines are available at their website and include a primer on EBM. Organizations such as the Cochrane Collaboration, EAST, the Society of Critical Care Medicine,

Infectious Disease Society of America, and many others are now trying to make EBM obtainable to all in an organized fashion that is reliable and easy to use. These organizations have attempted to rate further the quality of evidence and the strength of recommendations. The methods by which they have attempted to grade evidence and recommendations are illustrated in Table 2 [30-32]

Conclusions

One would be remiss to say that EBM and its practice is a product of physicians alone. Technology has had a large role in the advancement of EBM. Computers and database software allow compilation of large amounts of data. The Index Medicus has become a medical dinosaur of the past that students of today likely do not even recognize. The Internet has also allowed incredible access to masses of data and information. However, we must be careful with an overabundance of "unfiltered" data. As history as clearly shown us, evidence and data does not immediately translate into evidence-based practice.

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