Contents available at **PubMed**
www.anmm.org.mx

PERMANYER

Gac Med Mex. 2016;152:220-4

Iatrogenesis. From Iatromancy to Evidence-Based Medicine, to Iatromancy…

*Alberto Campos**
Faculty of Medicine, UNAM; General Director, Fundación Carlos Slim, Mexico City, Mexico

Abstract

The qualities of what is considered evidence change and evolve according to theoretical tools of analysis, but also with what the physician perceives and processes cognitively. This includes models and tools such as statistics and evidence-based medicine. Under the term 'iatromancy' are included here different ways of making inductive inferences to establish diagnoses, be it the divinatory art, heuristics, statistics, Evidence-based Medicine (EBM), or the "clinical eye". The interrelationships of different kinds of experience are discussed as justifications for the beliefs of physicians to form judgments in the decision-making processes. (Gac Med Mex. 2016;152:220-4)

Corresponding author: *Alberto Campos, alberto_campos@hotmail.com; http://orcid.org/0000-0001-5811-1908*

KEY WORDS: *Iatrogenic Disease. Iatromancy. Evidence-based Medicine.*

One of the most important distinctions of our judgments is, that some of them are intuitive, others grounded on argument. It is not in our power to judge as we will. The judgment is carried along necessarily by the evidence, real or seeming, which appears to us at the time[1].

Introduction: evidence

Why do we believe what we believe? One can say that a *p* statement is true because there is evidence of it but, what type of things (facts, data) are evidence? Under what conditions is a *p* statement supported by evidence? What does it mean to have evidence to infer that $p \rightarrow q$, i.e., that if a fact *p* occurs, then a fact *q* occurs? The sole logical or probabilistic connection between evidence and belief is not enough to infer that $p \rightarrow q$. It is necessary to understand the connection between *p* and the evidence of *p*. If so, then, what does it mean to have evidence of something, to have memory of previous perceptions? Under what circumstances, intuitive or rational, do we justify our evidence? Does knowing something imply that that something is true? And, when making a decision, how objective is our insight?

The purpose of this essay is to think what constitutes evidence, using iatromancy, insofar as the physician's vision, as a guiding thread. The term '*iatromancy*' has evolved since antiquity, from the divinatory arts of fortunetellers to the interpretation of our perception of what evidence constitutes in medicine, as a personal confrontation of statistics with clinical medicine. The feasibility for clinical intuitions and iatrogenesis to be eliminated by means of analytical tools is analyzed.

Correspondence:
*Alberto Campos
Unidad de Posgrado
Edificio A, 1.er piso, Circuito de Posgrados, Ciudad Universitaria
C.P. 04510, Ciudad de México, México.
E-mail: alberto_campos@hotmail.com
https://orcid.org/0000-0001-5811-1908

Date of reception: 20-01-2015
Date of acceptance: 12-02-2015

Iatromancy: from Babylon to the Hippocratic corpus

The earliest written evidence on relationships between physical and social events as a sign of the will of supranatural beings comes from Mesopotamia, around the year 2000 B.C., with the first records of laws, medicine and omens, in the form of systematic lists of correlations of events in clay tablets[2]. Mesopotamian medicine was a combination of symbolic manipulations, ritual representations and exorcisms against endless demons that caused diseases and other disasters, but it also involved material actions, prescription-based treatments and manipulations of the body.

In ancient Babylon, prescriptions resulting from iatromancy implied considerable training and a good dose of empirical evidence. The tablets, which were fundamental to establish the prognosis, were not a simple collection of omens, but a compilation of scholarly knowledge[3]. Diagnostic tablets with signs and symptoms were also used, and patient examination was essential to establish when, or not, to apply certain remedies. First hand observations were fundamental[4]. Omens had a specific conditional form: the first part, or protasis, expressed an observation, "if *p*", and the second part, the apodosis, the prediction, "then *q*"[5], which in logic is known as *modus ponens*. Similar to contemporary evaluation, the result and the consequences were the product of tabulation between good and evil[6]. However, for the purposes of our reflection, omens could be, at the same time, logically valid and false.

In ancient Greece, the belief in divine interventions as causes of diseases was rejected. The great achievement of Greek medicine was to establish that disease was not due to the will of any god, but to natural causes. The art (τέχνη, *téchne*) was established as a set of methodically organized procedures that required knowledge of nature (φύσις, *phýsis*) and the cause (αἰτίαι, *aítíai*) of disease. Art results from reasoning (λογισμός, *logismós*), rather than from luck (τύχη, *týche*) or philosophy (φιλοσοφίη). Additionally, it requires another quality: accuracy (ἀχρίβεια, ácríbeia)[7].

From statistics to Evidence-based Medicine (EBM)

Already since Hippocrates *Aphorisms* there are clues of rudimentary statistical principles as predictive instruments based on the records of observations. For example, out of one of these observations, today worryingly current, the author infers that "persons who are naturally very fat are apt to die earlier than those who are slender"[8 I].

There are testimonies from the time of Galen on the controversy between dogmatists (rationalists) and empiricists. His book *On Medical Experience* is an account where rationalists argue that experience not organized by reason is too chaotic to provide any understanding at all, to which empiricist reply that, either by observation (*autopsy*) or by confirmed testimonies (*history*), event concatenations emerge, from which it is possible to extract knowledge[9]. In this book, Galen affirms his belief on a combination of reason and experience as an adequate basis for medical knowledge; however, as we shall later see, tension between both, reason and experience, persists.

To quote just one experimental or, modestly put, empirical attempt between treatments, I shall mention that, in the 16th century, Ambroise Paré used to compare different treatments in soldiers who had sustained gunpowder burns. However, the term statistics (from Italian *statista*, statesperson), with the currently known meaning, originated later, in 18th century Germany, to describe the science of the State (*die Staatswissenschaft*)[10].

In the 19th century, Pierre-Charles-Alexandre Louis published a comparison of mortality in early-treated patients by means of bloodletting, and advocated for the *méthode numerique* (the numerical method) to assess treatment efficiency, instead of accepting medical opinions as standard test. Statistical tables can be claimed as being the first challenge to the Hippocratic medicine model in more than 2000 years. By the end of 19th century, statistics imposes over intuition, the quantitative over the qualitative[11].

The introduction of statistical and probabilistic methods in the USA into the field of epidemiology, and Boolean logic in the analysis of clinical practice, marked a new way to direct medical decision processes. Also crucial were the development of the Canadian public health system in the decade of 1960 and the foundation of the McMaster University School of Medicine and its problem-based learning program, which, in addition, included biostatistics; all as "the critical assessment of clinical information pertaining to the selection and interpretation of diagnostic tests, the study of etiology and causation, the interpretation of investigation of the clinical course and natural history of human disease, the assessment of therapeutic claims and the interpretation of studies of the quality of clinical care"[12].

I. Translated by A. Campos.

Evidence-based medicine (EBM) is a model intended to assess the relationship between different therapies according to evidence amenable to standardization. Thought since its origin as a "new paradigm", the model was created to turn medicine into an "objective and scientific endeavor". It was conceived for the clinical scenario of "a young resident in a teaching hospital" and it "requires skills that include efficient literature search and application of evidence formal rules in the assessment of clinical literature". Furthermore, EBM "de-emphasizes [sic] pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research"[13]. It defines itself as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients"[14]. Here, from its beginning, we find tension between the formal rules of evidence in the assessment of clinical literature and pathophysiological rationality, precisely an intuitive form of clinical judgment.

In spite of the use of powerful computers and online digital databases, and perhaps because of them, as quantification –but also evaluation– instruments, achievement of the aims of EBM is not trouble-free; moreover, it generates inherent problems. The translation of its own methodology into practice is one of them. We shall look into it later.

It is clear that, for EBM and the recommendation categories deriving from it, the results of clinical trials is what counts, which are adequate if and only if they involve, in addition to statistics, randomized controls (randomized controlled trials, RCT)[II] and, in addition, weight is taken away to non-randomized trials. The strong argument for the RTCs' epistemic superiority is that they "are alleged to solve the problem of 'unknown factors': a randomized trial is –allegedly– controlled for all factors known and *unknown*"[15 III]. In the discussion, I shall address this alleged epistemic superiority to solve unknown factors.

There are also discrepancies when data obtained through RCTs are compared to those from non-randomized historical trials (NRHT) with historical controls. Comparisons may show increases, decreases or no difference, which indicates that RCTs are also not without failure and, therefore, it is difficult to assume that they are closer to the truth than NRHTs. Randomization aside, there are other failures, such as, for example, comparisons across several interventions, studies with poor quality systematic review of data and inadequately concealed random allocation, which allows for the distribution of treatment arms to be subverted by participants or investigators[16].

Now, the EBM model does not comprise only RCTs and their analysis, but also synchronic cutoffs in the trials to assess intermediate points and decide whether to continue or stop the trial. It is there, at the intermediate points, where the standards of evidence to be considered are fixed. On the other hand, case reports can be evidence and a starting point of a research program; a good example of this is the first report on male homosexuals infected with *Pneumocystis carinii*, which marked the launch of the research program on HIV-AIDS[17]. There are also causative studies on diseases, for example new cases, cohort studies, as well as therapeutic trials where continuing with a placebo group can turn out to be a moral issue[16]. This is a very serious problem, since the development of a double-blind, randomized protocol where a placebo is included may well cause maleficence to the participants, a specific type of iatrogenesis that goes beyond the scope of this assay.

Contemporary iatromancy

One would think that the term *iatromancy* has to do only with ancient times' divinatory practices, but this is but this is not so. Actually, the Greek etymology is 'ιατρόμαντις (*iatrómantis*, from 'ιατρός, *iatrós*, 'he who heals' and μάντις, *mantis*, 'seer'), but the contemporary meaning of the term does not refer to omens, but to how the physician sees what she sees, how does she interpret what she perceives from the patient and forms a mental image; to use another contemporary expression, the "clinical eye".

Even in a different sense, we can say that a guess -a conjecture- as a decision process is generated from deficient knowledge under conditions of uncertainty, when we have to make decisions by means of heuristics, in a pressing context of risk. It is then when we can construct inductive propositions of the type if *p*, then *q*, from a systematization of signs and symptoms; however, the problem remains that of how to attribute some degree of certainty to inductive propositions for the prediction of contingent and random events based on the experience of past regularities. On one hand, we have no way to specify how many observations are required before empirical connections acquire meaning or what an adequate theory is and, on the other, the common individual does learn by simple clusters of

II. I use RCTs, as customary in international literature.
III. *Italics* in the original.

previous experiences; for her, the *empeiria* is observation and memory of things she has frequently seen happen and, similarly, that which somehow also includes testimonial knowledge. Thus, the tension between medicine based on personal experience and medicine based on statistical evidence comes to light.

Discussion: epistemic considerations

The fact of overrating RCTs with regard to non-statistical experience is an issue not without problems. One of them can be what does objectively constitute the best evidence available, since there are also methodological problems inherent to the analysis of RCTs, starting with a bad indexation that leads to incomplete and inefficient searches, which also renders meta-analytical studies incomplete. Another bias is not including systematic comparisons of RCTs with cohort studies, case reports or with large databases of health management services[16].

Certainly, evidence, the set of data we have on a medical fact, can be inaccurate and of provisional value; it is also true that the signs we see in a patient and biochemical parameters may not correspond to a real state of things, they may be transient or due to laboratory errors or to biological variability between patients. Then, during the medical act, face-to-face with the patient, it is necessary to mediate between statistical evidence in mind and the evidence facing the clinician. Why? Because, in terms of biological variability, the latter cannot always be subsumed in the former; each patient can be a black swan without the physician knowing it.

Frequently, meta-analyses allow for some well demarcated aspect of a problem to be seen, but not the problem as a whole. In the first place, because they are constructs, studies of studies, which in addition are not entirely but partially comparable to each other; secondly, they cannot *per se* account for the complexity that is characteristic of biological phenomena. In medicine, to account for complex phenomena, a multitude of RCTs have to be related to other type of histopathological, physiological, clinical, epidemiological observations that are not necessarily randomized.

The other side of the coin is that the rationale of medical evidence cannot be given by mere social practices or conventions, as some ideologies that call themselves in many ways, such as inclusive, traditional, multicultural, etc., pretend. Although conventions vary with different cultures, systematic analyses of data indicate that there are more or less common biological effects with particular causes. That is what is valuable as medical evidence, and not some community's cultural standards. Although some medical techniques of a certain community may have some degree of efficacy, their evidence beyond a collective placebo effect still requires validity for different and larger biological communities than the particular cultural communities they include. That is the achievement of the analytical tools EBM holds on to. It is important to insist here, systematic analyses, not large series or data collections. It also seems abusive to me, to designate a model as a "new paradigm". Although randomized controlled trials (and these trials' analyses) provide information on causal chains, that doesn't make them constitutive of theories, nor do they completely invalidate, in a Popperian sense, existing theories.

Now, another problem: with regard to the cognoscente subject, it is not clear how EBM can solve the previously mentioned unknown factors[15]. The association of powerful tools such as statistics, probability calculations and Boolean associations does not *per se* justify a belief, as their unconditional supporters claim, nor is it a complete answer to the nature of medical knowledge. Moreover, quantifications of the frequencies of phenomena indicate associations of events, but not causal explanations; Hume´s problem with regard to causality is still relevant today.

EBM does not explain what relationship there is between a belief, the type of evidence that supports it and the probability for it to be true; a good example of this is the publication "Effects of remote, retroactive, intercessory prayer on outcomes in patients with bloodstream infection: randomized controlled trial", to demonstrate that randomization is not enough for a study to reflect a condition of truth[19].

Sometimes, in the face of a problem of decision, we postpone judgment until we decide our behavior. Some propositions (or options) seem true or evident in themselves, of common sense, golden rules. The problem is that in medicine, which is characterized by individual variability, there is no room for axiomatic inferences, probabilities are not truths and certainties have degrees.

On the other hand, the fact that the randomization method is "never touched by the hand of man" does not guarantee the cleanliness of the protocol or its epistemic value, nor does it prevent (and even could favor) nominal value (at face value) interpretations of those who accept a publication in a flatest sense just because the title includes the expression "randomized controlled trial" (for an example, *cf.* Leibovici)[19].

Randomization is not a *sufficient* condition to reflect the condition of truth. But it is also questionable whether randomization is a *necessary* condition, i.e., whether it is true that we cannot obtain genuine evidence unless it has been validated by a duly randomized protocol[15].

On the other hand, the physician, who, with limited knowledge on statistical procedures trusts meta-analyses and the EBM model, may think that the outcome of a duly randomized protocol is not attributable to other cause than the treatment assessed, that, as intended by the model, all subjective condition of the assessment can be elliminated. That which it promises is precisely the type of certainty an RCT cannot provide, for several reasons: first, because asepsis in protocols is a utopia of *the* scientific method, although, nonetheless, we should not give up on this goal; second, because the final assessor of both the study and of that what it attempts to reflect, is the final reader, the physician who will use the study as a filter of what's false and true when being in front of the patient; third, because randomization *per se* cannot account for biological phenomena multiple causality, or for all phenomena that may concur in a patient; fourth, because EBM meta-analyses cannot account for whatever they not include, i.e., for those portions of reality that, due to the very nature of the data selection process for a specific meta-analysis, were not selected. Therefore, EBM may not account well for the biological phenomenon the physician has in front every time she assesses a patient and a medical act. There is no sure epistemic status.

It is important to understand what is to be understood by evidence and what kind of evidence both RCTs and meta-level analyses provide. That is the double problem the physician is permanently confronted with, whether her justified beliefs are enough to explain the causes of the disease of a particular patient and whether she can sufficiently justify her beliefs with RCT meta-analyses-based medical evidence, favoring this type of evidence over her medical experience.

On one hand, even if there is a meta-analysis for a problem we are addressing, it may not be available to us at the required moment; on the other, although mathematical analyses are powerful tools, they can be surpassed at the clinical moment by good judgment, which in a particular case can account for an exceptional event. This good judgment has its foundation on experience, not on statistics, and if in the EBM model the expert opinion has the least reliable degree of recommendation, to avoid the bias of non-revisable and allegedly infallible knowledge, the good, non-expert clinician, modest in her judgment, may well determine when a problem exceeds her capacity to solve it; she will always be able to resort to another physician, and this is not iatromancy, but good judgment.

Although uncertainty is unavoidable and the risk for iatrogenesis goes implicit in it, prudent judgment is not inevitable. Good medical practice requires the combination of evidence and experience, but the latter is acquired with the passage of time.

References

1. Reid T. On Judgment. En: Essays on the Intellectual Powers of Man. 1785, pp. 555-75. Eighteenth Century Collections Online. Gale. UNAM-ECCO.
2. Veldhuis N. Divination: Theory and Use. En: Guinan AK, Ellis MJ, Ferrara AJ, et al. If a Man Builds a Joyful House: Assyriological Studies in Honor of Erle Verdun Leichty. Leiden: Brill; 2006. p. 487-97.
3. Worthington M. Some Notes on Medical Information outside the Medical Corpora. En: Attia A, Buisson G. Advances in Mesopotamian Medicine from Hammurabi to Hippocrates. Leiden: Brill; 2009. p. 47-77.
4. Scurlock JA, Burton RA. Diagnoses in Assyrian and Babylonian Medicine: Ancient Sources, Translations, and Modern Medical Analyses. Urbana, IL, EE.UU.: University of Illinois Press; 2005.
5. Rochberg F. «If p, then q»: Form and Reasoning in Babylonian Divination. En: Annus A, ed. Divination and Interpretation of Signs in the Ancient World. Ann Arbor, MI, EE.UU.: The Oriental Institute, University of Chicago; 2010. p. 15-27.
6. Michalowski P. How to Read the Liver—In Sumerian. En: Guinan AK, Ellis MJ, Ferrara AJ, et al. If a Man Builds a Joyful House: Assyriological Studies in Honor of Erle Verdun Leichty. Leiden: Brill; 2006. p. 247-57.
7. Schiefsky MJ. Hippocrates on Ancient Medicine. Leiden: Brill; 2005. p. 1-18.
8. Aphorisms (II: 44). En: Hippocrates. Collected Works IV. Jones WHS, ed., trad. Cambridge, MA: Harvard University Press; 1959. p. 118-9.
9. Rabinowitz I. Galen, on Medical Experience. First Edition of the Arabic Version with English Translation and Notes by R. Walzer. The American Journal of Philology. 1949;70:437-40.
10. Diamandopoulos AA, Goudas CP, Kassimatis IT. Early Evidence-Based Medicine. The American Statistician. 2007;61:154-8.
11. Wootton D. Counting. En: Bad Medicine. Doctors Doing Harm Since Hippocrates. Oxford: Oxford University Press; 2006. p. 153-76.
12. Zimerman AL. Evidence-Based Medicine: A Short History of a Modern Medical Movement. Virtual Mentor. 2013;15(1):71-6.
13. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA. 1992;268(17):2420-5.
14. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996;312 (7023):71-2.
15. Worrall J. Evidence in Medicine and Evidence-Based Medicine. Philosophy Compass. 2007;2/6:981-1022.
16. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomized and non-randomized clinical trials. BMJ. 1998;317(7167):1185-90.
17. Centers for Disease Control (CDC). Pneumocystis pneumonia--Los Angeles. MMWR Morb Mortal Wkly Rep. 1981;30(21):250-2.
18. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6): 493-505.
19. Leibovici L. Effects of remote, retroactive, intercessory prayer on outcomes in patients with bloodstream infection, randomized controlled trial. BMJ. 2001;323(7327):1450-1.