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A brief history of medicine and statistics

History is a pack of lies about events that never happened told by people who weren't there. Those who cannot remember the past are condemned to repeat it.

George Santayana (1863–1952)

Learning objectives

In this chapter, you will learn:

- a brief history of medicine and statistics
- the background to the development of modern evidence-based medicine
- how to put evidence-based medicine into perspective

Introduction

The American health-care system is among the best in the world. Certainly we have the most technologically advanced system. We also spend the most money. Are we getting our money's worth? Are our citizens who have adequate access to health care getting the best possible care? What are the elements of the best possible health care, and who defines it? These questions can be answered by the medical research that is published in the medical literature. When you become an effective and efficient reader of the medical literature, you will be able to answer these questions. It is this process that we will be discussing in this book. This chapter will give you a historical perspective for learning how to find and use the best evidence in the practice of medicine.

Evidence-based medicine (EBM) is a new paradigm for the health-care system involving using the current evidence (results of medical research studies) in the medical literature to provide the best possible care to patients. What follows is a brief history of medicine and statistics, which will give you the historical basis and philosophical underpinnings of EBM. This is the beginning of a process designed to make you a more effective reader of the medical research literature.

Table 1.1. The basis of healing systems in different civilizations

Civilization	Energy	Elements
European	Humors	Earth, air, choler (yellow bile), melancholia (black bile)
East Indian	Chakras	Spirit, phlegm, bile
Chinese	Qi	Earth, metal, fire, water, wood
Native American	Spirits	Earth, air, fire, water

Prehistory and ancient history

Dawn of civilization to about AD 1000

Prehistoric man looked upon illness as a spiritual event. The ill person was seen as having a spiritual failing or being possessed by demons. Medicine practiced during this period and for centuries onward focused on removing these demons and cleansing the body and spirit of the ill person. Trephination, a practice in which holes were made in the skull to vent evil spirits or vapors, and religious rituals were the means to heal. With advances in civilization, healers focused on "treatments" that seemed to work. They used herbal medicines and became more skilled as surgeons.

About 4000 years ago, the Code of Hammurabi listed penalties for bad outcomes in surgery. In some instances, the surgeon lost his hand if the patient died. The prevailing medical theories of this era and the next few millennia involved manipulation of various forms of energy passing through the body. Health required a balance of these energies. The energy had different names depending on where the theory was developed. It was *qi* in China, *chakras* in India, humors in Europe, and natural spirits among Native Americans. The forces achieving the balance of energy also had different names. Each civilization developed a healing method predicated on restoring the correct balance of these energies in the patient, as described in Table 1.1.

The ancient Chinese system of medicine was based upon the duality of the universe. Yin and yang represented the fundamental forces in a dualistic cosmic theory that bound the universe together. The *Nei Ching*, one of the oldest medical textbooks, was written in about the third century BC. According to the *Nei Ching*, medical diagnosis was done by means of "pulse diagnosis" that measured the balance of *qi* (or energy flow) in the body. In addition to pulse diagnosis, traditional Chinese medicine incorporated the five elements, five planets, conditions of the weather, colors, and tones. This system included the 12 channels in which the *qi* flowed. Anatomic knowledge either corroborated the channels or was ignored. Acupuncture as a healing art balanced yin and yang by insertion of needles into the energy channels at different points to manipulate the *qi*. For the

Chinese, the first systematic study of human anatomy didn't occur until the mid eighteenth century and consisted of the inspection of children who had died of plague and had been torn apart by dogs.

Medicine in ancient India was also very complex. Medical theory included seven substances: blood, flesh, fat, bone, marrow, chyle, and semen. From extant records, we know that surgical operations were performed in India as early as 800 BC, including kidney stone removal and plastic surgery, such as the replacement of amputated noses, which were originally removed as punishment for adultery. Diet and hygiene were crucial to curing in Indian medicine, and clinical diagnosis was highly developed, depending as much on the nature of the life of the patient as on his symptoms. Other remedies included herbal medications, surgery, and the "five procedures": emetics, purgatives, water enemas, oil enemas, and sneezing powders. Inhalations, bleeding, cupping, and leeches were also employed. Anatomy was learned from bodies that were soaked in the river for a week and then pulled apart. Indian physicians knew a lot about bones, muscles, ligaments, and joints, but not much about nerves, blood vessels, or internal organs.

The Greeks began to systematize medicine about the same time as the *Nei Ching* appeared in China. Although Hippocratic medical principles are now considered archaic, his principles of the doctor–patient relationship are still followed today. The Greek medical environment consisted of the conflicting schools of the dogmatists, who believed in medical practice based on the theories of health and medicine, and the empiricists, who based their medical therapies on the observation of the effects of their medicines. The dogmatists prevailed and provided the basis for future development of medical theory. In Rome, Galen created popular, albeit incorrect, anatomical descriptions of the human body based primarily on the dissection of animals.

The Middle Ages saw the continued practice of Greek and Roman medicine. Most people turned to folk medicine that was usually performed by village elders who healed using their experiences with local herbs. Other changes in the Middle Ages included the introduction of chemical medications, the study of chemistry, and more extensive surgery by those involved with Arabic medicine.

Renaissance and industrial revolution

The first medical school was started in Salerno, Italy, in the thirteenth century. The Renaissance led to revolutionary changes in the theory of medicine. In the fifteenth century, Vesalius repudiated Galen's incorrect anatomical theories and Paracelsus advocated the use of chemical instead of herbal medicines. In the sixteenth century, the microscope was developed by Janssen and Galileo and popularized by Leeuwenhoek and Hooke. In the seventeenth century, the theory of

the circulation of blood was proposed by Harvey and scientists learned about the actual functioning of the human body. The eighteenth century saw the development of modern medicines with the isolation of foxglove to make digitalis by Withering, the use of inoculation against smallpox by Jenner, and the postulation of the existence of vitamin C and antiscorbutic factor by Lind.

During the eighteenth century, medical theories were undergoing rapid and chaotic change. In Scotland, Brown theorized that health represented the conflict between strong and weak forces in the body. He treated imbalances with either opium or alcohol. Cullen preached a strict following of the medical orthodoxy of the time and recommended complex prescriptions to treat illness. Hahnemann was disturbed by the use of strong chemicals to cure, and developed the theory of homeopathy. Based upon the theory that like cures like, he prescribed medications in doses that were so minute that current atomic analysis cannot find even one molecule of the original substance in the solution. Benjamin Rush, the foremost physician of the century, was a strong proponent of bloodletting, a popular therapy of the time. He has the distinction of being the first physician in America who was involved in a malpractice suit, which is a whole other story. He won the case.

The birth of statistics

Prehistoric peoples had no concept of probability, and the first mention is in the Talmud, written between AD 300 and 400. This alluded to the probability of two events being the product of the probability of each, but without explicitly using mathematical calculations. Among the ancients, the Greeks believed that the gods decided all life and, therefore, that probability did not enter into issues of daily life. The Greek creation myth involved a game of dice between Zeus, Poseidon, and Hades, but the Greeks themselves turned to oracles and the stars instead.

The use of Roman numerals made any kind of complex calculation impossible. Numbers as we know them today, using the decimal system and the zero, probably originated around AD 500 in the Hindu culture of India. This was probably the biggest step toward being able to manipulate probabilities and determine statistics. The Arabic mathematician Khowarizmi defined rules for adding, subtracting, multiplying, and dividing in about AD 800. In 1202, the book of the abacus, *Liber abaci* by Leonardo Pisano (more commonly known as Fibonacci), first introduced the numbers discovered by Arabic cultures to European civilization.

In 1494, Luca Paccioli defined basic principles of algebra and multiplication tables up to 60×60 in his book *Summa de arithmetica, geometria, proportioni e proportionalita.* He posed the first serious statistical problem of two men playing a game called balla, which is to end when one of them has won six rounds.

However, when they stop playing A has only won five rounds and B three. How should they divide the wager? It would be another 200 years before this problem was solved.

In 1545, Girolamo Cardano wrote the books *Ars magna* (The Great Art) and *Liber de ludo aleae* (Book on Games of Chance). This was the first attempt to use mathematics to describe statistics and probability, and he accurately described the probabilities of throwing various numbers with dice. Galileo expanded on this by calculating probabilities using two dice. In 1619, a puritan minister named Thomas Gataker, expounded on the meaning of probability by noting that it was natural laws and not divine providence that governed these outcomes.

Other famous scientists of the seventeenth century included Huygens, Leibniz, and Englishman John Graunt, who all wrote further on norms of statistics, including the relation of personal choice and judgment to statistical probability. In 1662, a group of Parisian monks at the Port Royal Monastery wrote an early text on statistics and were the first to use the word probability. Wondering why people were afraid of lightning even though the probability of being struck is very small, they stated that the "fear of harm ought to be proportional not merely to the gravity of the harm but also to the probability of the event."[1] This linked the severity, perception, and probability of the outcome of the risk for the person involved.

In 1660, Blaise Pascal refined the theories of statistics and, with help from Pierre de Fermat, solved the balla problem of Paccioli. All of these theories paved the way for modern statistics, which essentially began with the use of actuarial tables to determine insurance for merchant ships. Edward Lloyd opened his coffee shop in London at which merchant ship captains used to gather, trade their experiences, and announce the arrival of ships from various parts of the world. One hundred years later, this endeavour led to the foundation of Lloyds of London, which began its business of naval insurance in the 1770s.

John Graunt, a British merchant, categorized the cause of death of the London populace using statistical sampling, noting that "considering that it is esteemed an even lay, whether any man lived 10 years longer, I supposed it was the same, that one of any 10 might die within one year." He also noted the reason for doing this: to "set down how many died of each [*notorious disease*] . . . those persons may better understand the hazard they are in."[2] Graunt's statistics can be compared to recent data from the United States in 1993 in Table 1.2. As a result of this work, the government of the United Kingdom set up the first government-sponsored statistical sampling service.

With the rise in statistical thinking, Jacob Bernoulli devised the law of large numbers, which stated that as the number of observations increased the actual

[1] P. L. Bernstein. *Against the Gods: the Remarkable Story of Risk*. New York, NY: Wiley, 1998. p. 71.
[2] *Ibid.*, p. 82.

Table 1.2. Probability of survival: 1660 and 1993

	Percentage survival to each age	
Age, y	1660	1993
0	100%	100%
26	25%	98%
46	10%	95%
76	1%	70%

frequency of an event would approach its theoretical probability. This is the basis of all modern statistical inference. In the 1730s, Jacob's nephew Daniel Bernoulli developed the idea of utility as the mathematical combination of the quantity and perception of risk.

Modern era

Nineteenth century to today

The nineteenth century saw the development of Claude Bernard's modern physiology, William Morton's anesthesia, Joseph Lister and Ignatz Semmelweis' antisepsis, Wilhelm Roentgen's x-rays, Louis Pasteur and Robert Koch's germ theory, and Sigmund Freud's psychiatric theory. Changes in medical practice were illustrated by the empirical analysis done in 1838 by Pierre Charles Alexandre Louis. He showed that blood-letting therapy for typhoid fever was associated with increased mortality and changed this practice as a result. The growth of sanitary engineering and public health preceded this in the seventeenth and eighteenth centuries. This improvement had the greatest impact on human health through improved water supplies, waste removal, and living and working conditions. John Snow performed the first recorded modern epidemiological study in 1854 during a cholera epidemic in London. He found that a particular water pump located on Broad Street was the source of the epidemic and was being contaminated by sewage dumped into the River Thames. At the same time, Florence Nightingale was using statistical graphs to show the need to improve sanitation and hygiene in general for the British troops during the Crimean War. This type of data gathering in medicine was rare up to that time.

The twentieth century saw an explosion of medical technology. Specifics include the discovery of modern medicines by Paul Erlich, antibiotics (specifically sulfanilamide by Domagk and penicillin by Fleming), and modern

chemotherapeutic agents to treat ancient scourges such as diabetes (specifically the discovery of insulin by Banting, Best, and McLeod), cancer, and hypertension. The modern era of surgery has led to open-heart surgery, joint replacement, and organ transplantation. Advances in medicine continue at an ever-increasing rate.

Why weren't physicians using statistics in medicine? Before the middle of the twentieth century, advances in medicine and conclusions about human illness occurred mainly through the study of anatomy and physiology. The case study or case series was a common way to prove that a treatment was beneficial or that a certain etiology was the cause of an illness. The use of statistical sampling techniques took a while to develop. There were intense battles between those physicians who wanted to use statistical sampling and those who believed in the power of inductive reasoning from physiological experiments.

This argument between inductive reasoning and statistical sampling continued into the nineteenth century. Pierre Simon Laplace (1814) put forward the idea that essentially all knowledge was uncertain and, therefore, probabilistic in nature. The work of Pierre Charles Alexandre Louis on typhoid and diphtheria (1838) debunking the theory of bleeding used probabilistic principles. On the other side was Francois Double, who felt that treatment of the individual was more important than knowing what happens to groups of patients. The art of medicine was defined as deductions from experience and induction from physiologic mechanisms. These were felt to be more important than the "calculus of probability." This debate continued for over 100 years in France, Germany, Britain, and the United States.

The rise of modern biomedical research

Most research done before the twentieth century was more anecdotal than systematic, consisting of descriptions of patients or pathological findings. James Lind, a Royal Navy surgeon, carried out the first recorded clinical trial in 1747. In looking for a cure for scurvy, he fed sailors afflicted with scurvy six different treatments and determined that a factor in limes and oranges cured the disease while other foods did not. His study was not blinded, but as a result, 40 years later limes were stocked on all ships of the Royal Navy, and scurvy among sailors became a problem of the past.

Research studies of physiology and other basic science research topics began to appear in large numbers in the nineteenth century. By the start of the twentieth century, medicine had moved from the empirical observation of cases to the scientific application of basic sciences to determine the best therapies and catalog diagnoses. Although there were some epidemiological studies that looked at populations, it was uncommon to have any kind of longitudinal study of large

groups of patients. There was a 200-year gap from Lind's studies before the controlled clinical trial became the standard study for new medical innovations. It was only in the 1950s that the randomized clinical trial became the standard for excellent research.

There are three more British men who made great contributions to the early development of the current movement in EBM. Sir Ronald Fisher was the father of statistics. Beginning in the early 1900s, he developed the basis for most theories of modern statistical testing. Austin Bradford Hill was another statistician, who, in 1937, published a series of articles in the *Lancet* on the use of statistical methodology in medical research. In 1947, he published a simple commentary in the *British Medical Journal* calling for the introduction of statistics in the medical curriculum.[3] He called for physicians to be well versed in basic statistics and research study design in order to avoid the biases that were then so prevalent in what passed for medical research. Bradford Hill went on to direct the first true modern randomized clinical trial. He showed that streptomycin therapy was superior to standard therapy for the treatment of pulmonary tuberculosis.

Finally, Archie Cochrane was particularly important in the development of the current movement to perform systematic reviews of medical topics. He was a British general practitioner who did a lot of epidemiological work on respiratory diseases. In the late 1970s, he published an epic work on the evidence for medical therapies in perinatal care. This was the first quality-rated systematic review of the literature on a particular topic in medicine. His book *Effectiveness and Efficiency* set out a rational argument for studying and applying EBM to the clinical situation.[4] Subsequently, groups working on systematic reviews spread through the United Kingdom and now form a network in cyberspace throughout the world. In his honor, this network has been named the Cochrane Collaboration.

As Santayana said, it is important to learn from history so as not to repeat the mistakes that civilization has made in the past. The improper application of tainted evidence has resulted in poor medicine and increased cost without improving on human suffering. This book will give physicians the tools to evaluate the medical literature and pave the way for improved health for all. In the next chapter, we will begin where we left off in our history of medicine and statistics and enter the current era of evidence-based medicine.

[3] A. Bradford Hill. Statistics in the medical curriculum? *Br. Med. J.* 1947; ii: 366.
[4] A. L. Cochrane. *Effectiveness & Efficiency: Random Reflections on Health Services.* London: Royal Society of Medicine, 1971.

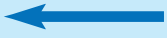
2

What is evidence-based medicine?

The most savage controversies are those about matters as to which there is no good evidence either way.

Bertrand Russell (1872–1970)

Learning objectives



In this chapter, you will learn:

- why you need to study evidence-based medicine
- the elements of evidence-based medicine
- how a good clinical question is constructed

The importance of evidence

In the 1980s, there were several studies looking at the utilization of various surgeries in the northeastern United States. These studies showed that there were large variations in the amount of care delivered to similar populations. They found variations in rates of prostate surgery and hysterectomy of up to 300% between similar counties. The variation rate in the performance of cataract surgery was 2000%. The researchers concluded that physicians were using very different standards to decide which patients required surgery. Why were physicians using such different rules? Weren't they all reading the same textbooks and journal articles? In that case, shouldn't their practice be more uniform?

> "Daily, clinicians confront questions about the interpretation of diagnostic tests, the harm associated with exposure to an agent, the prognosis of disease in a specific patient, the effectiveness of a preventive or therapeutic intervention, and the costs and clinical consequences of many other clinical decisions. Both clinicians and policy makers need to know whether the

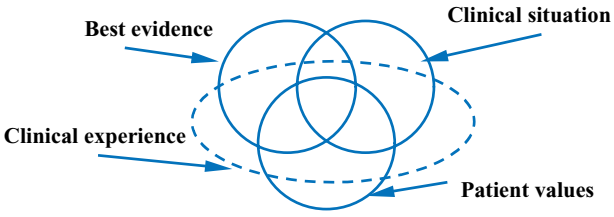


Fig. 2.1 The four elements to evidence-based health care: best available evidence, clinical situation, patient values and preferences, all bound together by clinical experience.

conclusions of a systematic review are valid, and whether recommendations in practice guidelines are sound."[1]

This is where Evidence-Based Medicine comes in.

Evidence-based medicine (EBM) has been defined as "the conscientious, explicit, and judicious use of the best evidence in making decisions about the care of individual patients" (http://ebm.mcmaster.ca/documents/how_to_teach_ebcp_workshop_brochure_2009.pdf).[2] The EBM stems from the physician's need to have *proven* therapies to offer patients. This is a paradigm shift that represents both a breakdown of the traditional hierarchical system of medical practice and the acceptance of the scientific method as the governing force in advancing the field of medicine. Simply stated, EBM is applying the best evidence that can be found in the medical literature to the patient with a medical problem, resulting in the best possible care for each patient. Evidence-based clinical practice (EBCP) is a definition of an approach to medical practice in which you the clinician are able to evaluate the strength of that evidence and use it in the best clinical practice for the patient sitting in your office.

Evidence-based medicine can be seen as a combination of three skills by which practitioners become aware of, critically analyze, and then apply the best available evidence from the medical research literature for the care of individual patients. The first of these is Information Mastery (IM), the skill of searching the medical literature in the most efficient manner to find the best available evidence. This skill will be the focus of Chapter 5. The majority of the chapters in this book will focus on the skill of Critical Appraisal (CA) of the literature. This set of skills will help you to develop critical thinking about the content of the medical literature. Finally, the results of the information found and critically appraised must be applied to patient care in the process of Knowledge Translation (KT), which is the subject of Chapter 17. The application of research results is a blend of the available evidence, the patient's preferences, the clinical situation, and the practitioner's clinical experience (Fig. 2.1).

[1] McMaster University Department of Clinical Epidemiology and Biostatistics. Evidence-based clinical practice (EBCP) course, 1999.
[2] D. L. Sackett, W. M. Rosenberg, J. A. Gray, R. B. Haynes & W. S. Richardson. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312: 71–72.