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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 what we are doing into perspective

This is the beginning' of a process designed to make you a more effective reader of the medical research literature. This chapter will give you a historical perspective for learning how to use the best evidence in the practice of medicine.

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 those of our citizens who have adequate access to health care getting the best possible care? What is the best possible health care and who defines it? These are some of the questions that we will be discussing in this book.

Evidence-based medicine is a new paradigm for the health-care system. It involves using the current evidence in the medical literature to provide the best possible care to patients. We search for the evidence needed to provide the best care for the patient. We measure the results by studying the health-care system and the specific outcomes of care given to patients. What follows is a brief history of medicine and statistics. This introduction will give you the historical basis and philosophical underpinnings of evidence-based medicine.

Table 1.1. The basis of healing systems in different civilizations

Civilization	Energy	Elements
Europe	Humors	Earth, air, choler (yellow bile), melancholia (black bile)
India	Chakras	Spirit, phlegm, bile
China	Qi	Earth, metal, fire, water, wood
Native America	Spirits	Earth, air, fire, water

Pre- 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/or spirit) of the ill person. Trephination (holes 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 (vegetable) medicines and became more skilled as surgeons.

About 4000 years ago, the Code of Hammurabi listed penalties for bad outcomes in surgery. 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* (*Nei Jing*), one of the oldest medical textbooks, was written about the third century BC. Medical diagnosis was done by means of "pulse diagnosis" that measured the balance of *qi* in the body. This system included the 12 channels in which the *qi* flowed. Anatomic knowledge either corroborated the channels or was ignored. The first systematic study of human anatomy didn't occur until the mid eighteenth century. It consisted of the inspection of children who had died of plague and been torn apart by dogs. In addition to the five elements, there were also five planets, conditions of the weather, colors, and tones. Acupuncture as a healing art balanced yin and

yang by insertion of needles into the energy channels at different points and manipulating the *qi*.

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 (replacement of amputated noses, the 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 considered archaic, his principles of the doctor–patient relationship are still followed today. In Rome, Galen created (incorrect) anatomical descriptions of the human body based primarily on the dissection of animals. The Middle (very dark) Ages saw the continued practice of Greek and Roman medicine. Most people turned to folk medicine that was usually performed by village elders (men or women) who healed using their experiences with local herbs. Arabic medicine introduced the use of chemical medications, the study of chemistry, and more extensive surgery.

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 vegetable medicines. From the sixteenth-century development of the microscope (Janssen and Galileo get the credit although Leeuwenhoek and Hooke made it popular) to the seventeenth-century theory of the circulation of blood (Harvey), scientists learned about the actual functioning of the human body. The eighteenth century saw the development of modern medicines with the isolation of foxglove (digitalis) by Withering, the use of inoculation (against smallpox) by Jenner, and the postulation of the existence of vitamins (vitamin C, 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 (another story, and he won).

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. 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 towards 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 (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 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, Thomas

Table 1.2. Probability of survival, 1660 and 1993

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

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 including Huygens (1657), Leibniz (1662), and Englishman John Graunt (1660) wrote further on norms of statistics, including the relation of personal choice and judgment to statistical probability. A group of Parisian monks at the Port Royal Monastery (1662) 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.

Blaise Pascal (1660) refined the theories of statistics and, with Pierre de Fermat, solved the balla problem of Paccioli. These all paved the way for modern statistics, which essentially began with the use of actuarial tables to determine insurance for merchant ships. This led to the foundation of Lloyds of London, which began its business of naval insurance in the 1770s. That was 100 years after Edward Lloyd opened his coffee shop in London at which merchant ship captains use to gather, trade their experiences, and announce the arrival of ships from various parts of the world.

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.

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

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 frequency of an event would approach its theoretical probability. This is the basis of all modern statistical inference. In the 1730s, Daniel Bernoulli (Jacob's nephew) 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 modern physiology (Bernard) anesthesia (Morton), antisepsis (Lister and Semmelweis), x-rays (Roentgen), the germ theory (Pasteur and Koch), and psychiatric theory (Freud). 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. 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 (Erlich), antibiotics (sulfanilamide by Domagk and penicillin by Fleming), and modern chemotherapeutic agents to treat ancient scourges like diabetes (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.

Pierre Simon Laplace (yes, the one of the famous law) put forward the idea (1814) that essentially all knowledge was uncertain and therefore probabilistic in nature. The work of Pierre Charles Alexandre Louis (1838) on typhoid and diphtheria showed that bleeding (the most important medical therapeutic tool of the time) was not beneficial in the treatment of these diseases. On the other side was Francois Double (1835) who felt that treatment of the individual was

more important that 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 (subsequently found to be vitamin C) cured the disease while other foods did not. His study was not blinded, but as a result (although not for 40 years) limes were stocked on all ships of the Royal Navy, and scurvy among sailors (limeys) 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 men (sorry, they were, and happened all to be British too) who made great contributions to the early development of the current movement in evidence-based medicine. 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 (antibiotic) therapy was superior to standard therapy for the treatment of pulmonary tuberculosis.

[3] A. Bradford Hill. Statistics in the medical curriculum? *Br. Med. J.* 1947; ii: 366.

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* (1971) 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 they form a network in cyberspace throughout the world. In his honor they have 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.

[4] A. L. Cochrane. *Effectiveness & Efficiency: Random Reflections on Health Services*. London: Royal Society of Medicine, 1971.

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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

What is so important about evidence

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."[1]

In the 1980s there were several studies of the utilization of various operations by the health-care system in the northeastern USA. These showed that there were large variations in the amount of care delivered to similar populations. These studies 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

[1] D. L. Sackett, W. M. Rosenberg, J. A. M. Gray, R. B. Haynes & W. S. Richardson. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312: 71–72.

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 conclusions of a systematic review are valid, and whether recommendations in practice guidelines are sound."[2]

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 the application of the best evidence that can be found in the medical literature to the patient with a medical problem. It should result in the best possible care given to each patient. **Evidence-based clinical practice (EBCP)** is 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.

Medical decision making: expert vs. evidence-based

Because of the scientific basis of medical research, evidence-based medical practice has been around for centuries. Its explicit application (as EBM) to problem solving in clinical medicine began simultaneously in the late 1980s at McMaster University in Canada and at Oxford University in the United Kingdom. In response to high variability of practice, increasing costs, and complexity of medical care, systems were needed to define the best (and cheapest) treatments. Individuals trained in both clinical medicine and epidemiology collaborated to develop strategies to assist in the critical appraisal of clinical data from the biomedical journals.

In the past, a physician faced with a "clinical predicament" would turn to a senior physician (expert) for the definitive answer to this problem. This could take the form of an informal discussion on rounds with the senior attending (consultant) physician, or the referral of a patient to a specialist. The answer would come from the more experienced (and usually older) physician, and would be taken at face value by the younger (and more inexperienced) physician. It was usually based upon the many years of experience of the older physician, but was not necessarily ever tested empirically.

Steps in practicing evidence-based medicine

There are six steps in the process of EBM. These steps are also called the educational prescription[3], and they are as follows:

[2] McMaster University Department of Clinical Epidemiology and Biostatistics. Evidence-based clinical practice (EBCP) course, 1999.
[3] Based on: W. S. Richardson. *Educational prescription: the five elements*. University of Rochester.