PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH

SECOND EDITION

EDITED BY

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Preface

The positive reception of the first edition of *Principles and Practice of Clinical Research* prompted the second edition, which was written in the context of continued growth and scope of clinical research as a discipline since the publication of the first edition in 2002. The course at the National Institutes of Health (NIH) Clinical Center, which led to the production of the first edition, has been in existence for ten years and is now taught to nearly 1,000 students annually at the NIH Clinical Center and at multiple long-distance learning sites, including both domestic and international partners.

This second edition includes new chapters on clinical research from a patient's perspective, managing conflicts of interest in clinical research, the clinical researcher and the media, clinical research from an industry perspective, data management in clinical research, how to evaluate a protocol budget, and the role of the human genome project and genomics in clinical research. All other chapters have been updated with extensive changes in the chapters on technology transfer and how to successfully navigate the NIH peer review process for grants.

We hope that this book provides the reader with an expanded awareness of the broad scope of clinical research and the tools to conduct such research safely and effectively. Our goals as investigators should be to strive to improve the well being of patients in general while ensuring the safety of our research subjects enrolled in investigational protocols.

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CHAPTER

1

A Historical Perspective on Clinical Research

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If I have seen a little further it is by standing on the shoulders of giants. —Sir Isaac Newton, 1676

The successful translation of a basic or clinical observation into a new treatment of disease is rare in an investigator's professional life, but when it occurs, the personal thrill is exhilarating and the impact on society may be substantial. The following historical highlights provide a perspective of the continuum of the clinical research endeavor. These events also emphasize the contribution that clinical research has made to advances in medicine and public health.

In this chapter, and throughout this book, a broad definition of clinical research of the Association of American Medical Colleges Task Force on Clinical Research is used.[1] That task force defined clinical research as

> a component of medical and health research intended to produce knowledge essential for understanding human disease, preventing and treating illness, and promoting health. Clinical research embraces a continuum of studies involving interaction with patients, diagnostic clinical materials or data, or populations, in any of these categories: disease mechanisms; translational research; clinical knowledge; detection; diagnosis and natural history of disease; therapeutic interventions including clinical trials; prevention and health promotion; behavioral research; health services research; epidemiology; and community-based and managed care-based research.

1. THE EARLIEST CLINICAL RESEARCH

Medical practice and clinical research are grounded in the beginnings of civilization. Egyptian medicine was dominant from approximately 2850 BC to 525 BC. The Egyptian Imhotep, whose name means "he who gives contentment," lived slightly after 3000 BC and was the first physician figure to rise out of antiquity.[2] Imhotep was a known scribe, priest, architect, astronomer, and magician (medicine and magic were used together), and he performed surgery, practiced some dentistry,[1] extracted medicine from plants, and knew the position and function of the vital organs.

There is also evidence that ancient Chinese medicine included clinical studies. For example, in 2737 BC Shen Nung, the putative father of Chinese medicine, experimented with poisons and classified medical plants,[3] and I. Yin (1176–1123 BC), a famous prime minister of the Shang dynasty, described the extraction of medicines from boiling plants.[4]

Documents from early Judeo-Christian and Eastern civilizations provide examples of a scientific approach to medicine and the origin of clinical research. In the Old Testament, written from the 15th century BC to approximately the 4th century BC,[5] a passage in the first chapter of the Book of Daniel describes a comparative "protocol" of diet and health. Daniel demonstrated the preferred diet of legumes and water made

for healthier youths than the king's rich food and wine:

> Then Daniel said to the steward . . .
> "Test your servants for ten days; let us be given vegetables to eat and water to drink. Then let your appearance and the appearance of the youths who eat the king's rich food be observed by you, and according to what you see deal with your servants:
> So he harkened to them in this matter; and tested them for ten days.
> At the end of ten days it was seen that they were better in appearance and fatter in flesh than all the youths who ate the king's rich food. So the steward took away their rich food and the wine they were to drink, and gave them vegetables."
> Daniel 1:11–16

The ancient Hindus also excelled in early medicine, especially in surgery, and there is evidence of Indian hospitals in Ceylon in 437 and 137 BC.[4]

2. THE GREEK AND ROMAN INFLUENCE

Although early examples of clinical research predate the Greeks, Hippocrates (460–370 BC) is considered the father of modern medicine, and he exhibited the strict discipline required of a clinical investigator.

His emphasis on the art of clinical inspection, observation, and documentation established the science of medicine. In addition, as graduating physicians are reminded when they take the Hippocratic oath, he provided physicians with high moral standards. Hippocrates' meticulous clinical records were maintained in 42 case records representing the first known recorded clinical observations of disease.[6] These case studies describe, among other maladies, malarial fevers, diarrhea, dysentery, melancholia, mania, and pulmonary edema with remarkable clinical acumen.

On pulmonary edema, he wrote the following:

> Water accumulates; the patient has fever and cough; the respiration is fast; the feet become edematous; the nails appear curved and the patient suffers as if he has pus inside, only less severe and more protracted. One can recognize that it is not pus but water . . . if you put your ear against the chest you can hear it seethe inside like sour wine.[7]

Hippocrates also described the importance of cleanliness in the management of wounds. He wrote, "If water was used for irrigation, it had to be very pure or boiled, and the hands and nails of the operator were to be cleansed."[8] Hippocrates' teachings remained dominant and unchallenged until Galen of Pergamum (ca. 130–200 AD), the physician to the Roman Emperor Marcus Aurelius.[9] Galen was one of the first individuals to utilize animal studies to understand human disease. By experimenting on animals, he was able to describe the effects of transection of the spinal cord at different levels. According to Galen, health and disease were the balance of four humors (blood, phlegm, black bile, and yellow bile), and veins contained blood and the humors, together with some spirit.[9]

3. MIDDLE AGES AND RENAISSANCE

In the Middle Ages, improvements in medicine became evident, and the infrastructure for clinical research began to develop. Hospitals and nursing, with origins in the teachings of Christ,[10] became defined institutions (although the forerunner of hospitals can be traced to the ancient Babylonian custom of bringing the sick into the marketplace for consultation, and the Greeks and Romans had military hospitals). By the 1100s and 1200s, hospitals were being built in England, Scotland, France, and Germany.

Early progress in pharmacology can be linked to the Crusades and the development of commerce. Drug trade became enormously profitable during the Middle Ages. Drugs were recognized as the lightest, most compact, and most lucrative of all cargoes. The influences of Arabic pharmacy and the contact of the Crusaders with their Moslem foes spread the knowledge of Arabic pharmaceuticals and greatly enhanced the value of drugs from the Far East. The records of the customhouse at the port of Acre (1191–1291) show a lively traffic in aloes, benzoin, camphor, nutmegs, and opium.[11]

Documentation through case records is an essential feature of clinical research. Pre-Renaissance medicine of the 14th and 15th centuries saw the birth of "Consilia" or medical-case books, consisting of clinical records from the practice of well-known physicians.[12] Hippocrates' approach of case studies developed 1700 years earlier was reborn, particularly in the Bolognese and Paduan regions of Italy. Universities became important places of medicine in Paris, Bologna, and Padua.

Clinical research remained mostly descriptive, resembling today's natural history and disease pathogenesis protocols. In 1348, Gentile da Foligno, a Paduan professor, described gallstones.[12] Bartolommeo Montagnana (1470), an anatomist, described strangulated hernia, operated on lachrymal fistula, and extracted decayed teeth.[12] There was also evidence of the beginning of a statistical approach to medical issues during this period. For example, a 14th-century letter from Petrach to Boccaccio states that

> I once heard a physician of great renown among us express himself in the following terms: . . . I solemnly affirm and believe, if a hundred or a thousand of men of the same age, same temperament and habits, together with the same

surroundings, were attacked at the same time by the same disease, that if the one half followed the prescriptions of the doctors of the variety of those practicing at the present day, and that the other half took no medicine but relied on Nature's instincts, I have no doubt as to which half would escape.[13]

The Renaissance (1453–1600) represented the revival of learning and transition from medieval to modern conditions; many great clinicians and scientists prospered. At this time, many of the ancient Greek dictums of medicine, such as Galen's four humors, were discarded. Perhaps the most important anatomist of this period was Leonardo da Vinci (1453–1519) (Fig. 1-1).[14] Da Vinci created more than 750 detailed anatomic drawings (Fig. 1-2).

4. SEVENTEENTH CENTURY

Studies of blood began in the 17th century. William Harvey (1578–1657) convincingly described the circulation of blood from the heart through the lungs and back to the heart and then into the arteries and back through the veins.[16] Harvey emphasized that the arteries and veins carried only one substance, the blood, ending Galen's proposal that veins carried a blend of multiple humors. (Of course, today we know that blood contains multiple cellular and humoral elements, so to some extent Galen was correct.) The famous architect Sir Christopher Wren (1632–1723), originally known as an astronomer and anatomist (Fig. 1-3), in 1656 assembled quills and silver tubes as cannulas and used animal bladders to inject opium into the veins of dogs.[17] The first well-documented transfusions of blood into humans were done in 1667 by Richard Lower and Edmund King in London[18] and mentioned in Pepys' diary.[19]

The 17th century also brought the first vital statistics, which were presented in Graunt's book, *Natural and Political Observations Mentioned in a Following Index, and Made Upon the Bills of Mortality*.[20] In this book of comparative statistics, populations and mortality sta-

FIGURE 1-1 Leonardo da Vinci self-portrait (red chalk); Turin, Royal Library. From reference 14, Figure 1.

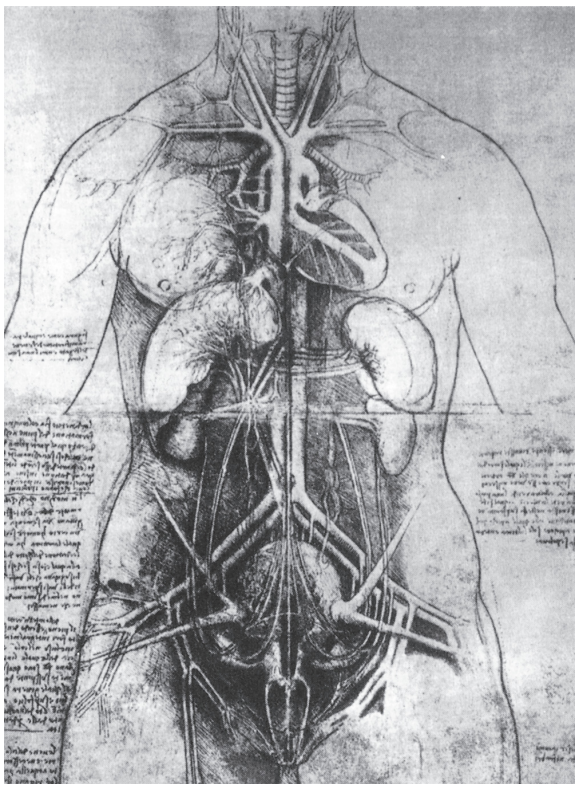


FIGURE 1-2 Example of anatomic drawing by Leonardo da Vinci. Trunk of female human body, with internal organs seen as though ventral side were transparent. From reference 14, p. 369.

tistics were compared for different countries, ages, and sex for rural and urban areas. The importance of using mortality among groups would have major importance in future clinical studies.

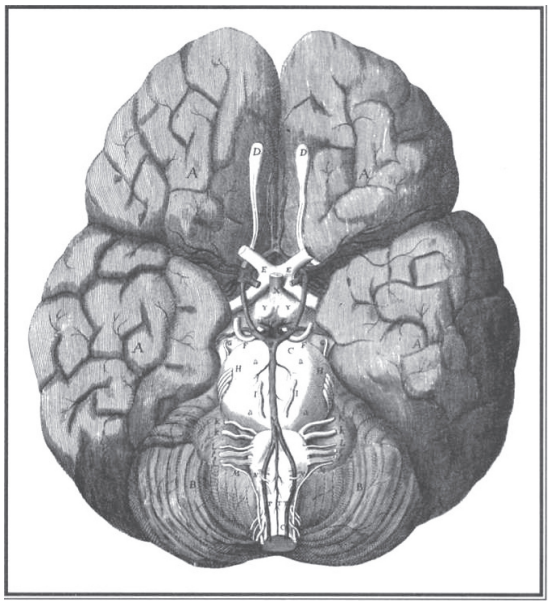


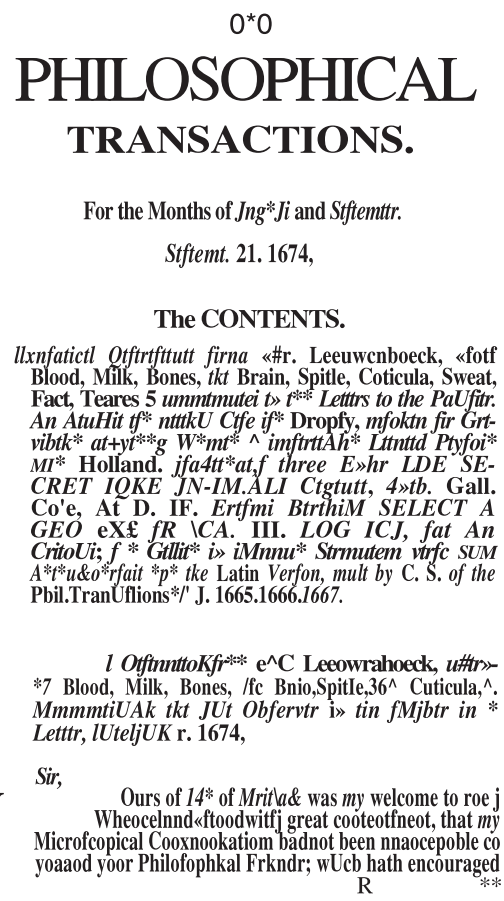
FIGURE 1-3 Christopher Wren's drawing of the brain shows blood vessels discovered by Thomas Willis.[15]

FIGURE 1-4 Antony van Leeuwenhoek. From reference 21.

5. EIGHTEENTH CENTURY

The 18th century brought extraordinary advances in the biological sciences and medicine. At the end of the 17th century, Antony van Leeuwenhoek of Delft (1632–1723) invented the microscope. Although he is best known for using his microscope to provide the first descriptions of protozoa and bacteria, Leeuwenhoek also provided the first description of striated voluntary muscle, the crystalline structure of the lens, red blood cells, and spermatozoa (Figs. 1-4 and 1-5).[21]

Modern clinical trials can be recognized in the 1700s. Scurvy was a major health problem for the British Navy. William Harvey earlier had recommended lemons to treat scurvy but argued that the therapeutic effect was a result of the acid in the fruit. James Lind (Fig. 1-6), a native of Scotland and a Royal Navy surgeon, conducted a clinical trial in 1747 to assess this hypothesis comparing three therapies for scurvy (Table 1-1).[22] Twelve sailors with classic scurvy were divided



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PHILOSOPHICAL

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FIGURE 1-5 Title page from Leeuwenhoeck's paper on *Microscopical Observations.* From reference 16.

FIGURE 1-6 James Lind.

TABLE 1-1 Treatment of Scurvy by James Lind

Treatment Arm	Cured	*p* Value[a]
Sulfuric acid	0/2	>0.05
Vinegar	0/2	>0.05
Seawater	0/2	>0.05
Cider	0/2	>0.05
Physicians	0/2	>0.05
Citrus fruit	2/2	>0.05

[a]Compared to patients in the five areas of the trial; no placebo group.

into six groups of two each, all given identical diets, and the various groups supplemented with vinegar, dilute sulfuric acid, cider, seawater, a nutmeg, garlic, and horseradish mixture, and with two oranges and one lemon daily.

Sulfuric acid, vinegar, seawater, cider, and physician's remedy had no benefit. Two sailors receiving citrus fruit avoided scurvy. Although not significant because of sample size, this early clinical study formed the basis for successfully avoiding scurvy with citrus fruit. The studies with sulfuric acid, vinegar, and cider excluded acid as a likely explanation for the beneficial effect of citrus fruit.

The 18th century saw great progress in the area of surgery. A remarkable succession of teachers and their students led these studies. Percival Pott of St. Bartholomew's Hospital described tuberculosis of the spine or "Pott's disease."[23] John Hunter, Pott's pupil, was the founder of experimental and surgical pathology as well as a pioneer in comparative physiology and experimental morphology. Hunter described shock, phlebitis, pyremia, and intussusception and made major findings of inflammation, gunshot wounds, and the surgical diseases of the vascular system.[23] Hunter's student, Edward Jenner (1749–1823),[23] introduced vaccination as a tool to prevent infectious diseases (Fig. 1-7).[24] Jenner was aware that dairymaids who had contacted cowpox through milking did not get smallpox. In 1798, Jenner conceived of applying the observation on a grand scale to prevent smallpox.[25]

Jenner was not the first to conceive of the idea of inoculation for smallpox. For example, the Chinese had thought of this earlier and Sir Hans Sloane had done small studies in 1717 using variolation (inoculating healthy people with pus from blisters obtained from patients with smallpox).[26] In addition, James Jurin published several articles between 1723 and 1727 comparing death from natural smallpox in people who had not been inoculated with those who had been inoculated. Jurin showed that death occurred in 5 of 6 subjects in the first group compared to 1 in 60 in the latter,[27] providing one of the first studies using mortality as a critical clinical end point. In 1734, Voltaire wrote, "The Cirassians [a Middle Eastern people] perceived that of a thousand persons hardly one was attacked twice by full blown smallpox; that in truth one sees three or four mild cases but never two that are serious and dangerous; that in a word one never truly has that illness twice in life."[28] Thus, Voltaire recognized natural immunity to smallpox, which was an important concept for future vaccinology. In 1721, Cotton Mather demonstrated that variolation protected citizens of the American colonies in Massachusettes,[29] and in 1777 George Washington used variolation against smallpox to inoculate the Continental Army, the first massive immunization of a military.[30] Jenner was the first to try vaccination on a large scale using scabs from cow pox to protect against human smallpox and the first to use experimental approaches to establish the scientific basis for vaccination. Jenner transformed a local country tradition into a viable prophylactic principle. Jenner's vaccine was adopted quickly in Germany and then in Holland, Denmark, the rest of Europe, and the United States.

FIGURE 1-7 Edward Jenner (painting by Sir Thomas Lawrence). From reference 3, p. 373.

The 1700s were also when the first known blinded clinical studies were performed. In 1784, a commission of inquiry was appointed by King Louis XVI of France to investigate medical claims of "animal magnetism" or "mesmerism." The commission, headed by Benjamin Franklin and consisting of such distinguished members as Antoine Lavoisier, Jean-Sylvain Bailly, and Joseph-Ignace Guillotin, had as a goal to assess whether the reported effects of this new healing method were due to "real" force or due to "illness of the mind." Among the many tests performed, blindfolded people were told that they were either receiving or not receiving magnetism when in fact, at times, the reverse was happening. The results showed that study subjects felt effects of magnetism only when they were told they received magnetism and felt no effects when they were not told, whether or not they were receiving the treatment.[31] This was the beginning of the use of blinded studies in clinical research.

The 18th century also provided the first legal example that physicians must obtain informed consent from patients before a procedure. In an English lawsuit, *Slater v. Baker & Stapleton*, two surgeons were found liable for disuniting a partially healed fracture without the patient's consent.[32] This case set the important precedent described by the court: "Indeed it is reasonable that a patient should be told what is about to be done to him that he may take courage and put himself in such a situation as to enable him to undergo the operation."

6. NINETEENTH CENTURY

In the first days of the 19th century, Benjamin Waterhouse, a Harvard professor of medicine, brought Jenner's vaccine to the United States, and by 1802 the first vaccine institute was established by James Smith in Baltimore, Maryland. This led to a national vaccine agency, which was established by the Congress of the United States under the direction of James Smith in 1813.[33]

Jenner's vaccination for smallpox was followed by other historic studies in the pathogenesis of infectious diseases. The French physician Pierre Charles Alexandre Louis (1787–1872) realized that clinical observations on large numbers of patients were essential for meaningful clinical research. He published classical studies on typhoid fever and tuberculosis, and his research in 1835 on the effects of bloodletting demonstrated that the benefits claimed for this popular mode of treatment were unsubstantiated.[34] On February 13, 1843, one of Louis' students, Oliver Wendell Holmes (1809–1894), the father of the great Justice Holmes, read his article, *On the Contagiousness of Puerperal Fever*,[35] to the Boston Society for Medical Improvement (Fig. 1-8). Holmes stated that women in childbed should never be attended by physicians who have been conducting postmortem sections on cases of puerperal fever; that the disease may be conveyed in this manner from patient to patient, even from a case of erysipelas; and that washing the hands in calcium chloride and changing the clothes after leaving a puerperal fever case was likely to be a preventive measure. Holmes' essay stirred up violent opposition by obstetricians. However, he continued to reiterate his views, and in 1855 in a monograph, *Puerperal Fever as a Private Pestilence*, Holmes noted that Semmelweis, working in Vienna and Budapest, had lessened the mortality of puerperal fever by disinfecting the hands with chloride of lime and the nail brush.[36]

Ignaz Philipp Semmelweis (1818–1865) performed the most sophisticated preventive clinical trial of the 19th century that established the importance of hand washing to prevent the spread of infection (Fig. 1-9).[37] Semmelweis, a Hungarian pupil, became an assistant in the first obstetric ward of the Allgemeines Kranken-

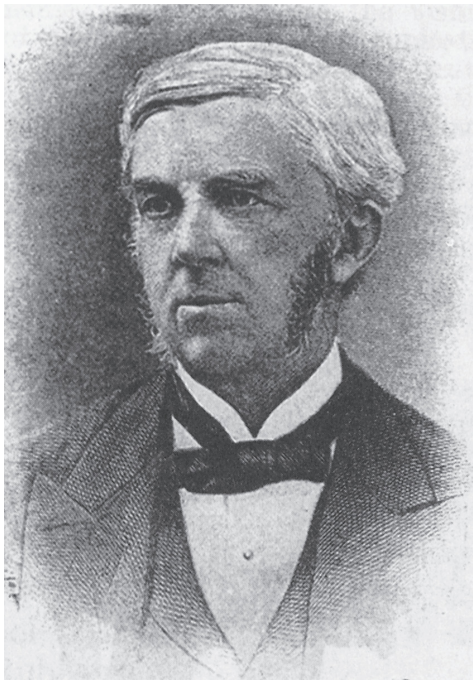

FIGURE 1-8 Oliver Wendell Holmes. From reference 3, p. 435.

haus in Vienna in 1846. Semmelweis was troubled by the death rate associated with puerperal or "childbed" fever. From 1841 to 1846, the maternal death rate from puerperal sepsis averaged approximately 10%, and in some periods as high as 50%, in the First Maternity Division of the Vienna General Hospital. In contrast, the rate was only 2 or 3% in the Second Division, which was attended by midwives rather than physicians. The public knew the disparity, and women feared being assigned to the First Division. Semmelweis became frustrated by this mystery and began to study cadavers of fever victims. In 1847, his friend and fellow physician, Jakob Kolletschka, died after receiving a small cut on the finger during an autopsy. The risk of minor cuts during autopsies was well-known, but Semmelweis made the further observation that Kolletschka's death was characteristic of death from puerperal fever. He reasoned that puerperal fever was "caused by conveyance to the pregnant women of putrid particles derived from living organisms, through the agency of the examining fingers." In particular, he identified the cadaveric matter from the autopsy room, with which the midwives had no contact, as the source of the infection.

In 1847, Semmelweis insisted that all students and physicians scrub their hands with chlorinated lime before entering the maternity ward, and during 1848 the mortality rate on his division dropped from 9.92%

FIGURE 1-9 Ignaz Philipp Semmelweis. From reference 4, p. 436.

to 1.27%. Despite his convincing data, his colleagues rejected his findings and accused him of insubordination. The dominant medical thinking at the time was that the high mortality in the charity hospital related to the poor health of the impoverished women, despite the difference between the control (no chlorinated lime hand washing) and experimental (washing with chlorinated lime) divisions. Without any opportunity for advancement in Vienna, Semmelweis returned to his home in Budapest and repeated his studies with the same results. In 1861, he finally published *The Etiology, Concept, and Prophylaxis of Childhood Fever*.[37] Although Holmes' work antedated Semmelweis by 5 years, the superiority of Semmelweis' observation lies not only in his experimental data but also in his recognition that puerperal fever was a blood poisoning. The observations of Holmes and Semmelweis were a critical step for medicine and surgery.

In addition to discovering the importance of hand washing, the first well-documented use of ether for surgery (1846) by William Thomas Green Morton with

Dr. John Collins Warren as the surgeon at the Massachusetts General Hospital also occurred during the 19th century.[38] Oliver Wendell Holmes is credited with proposing the words *anesthetic* and *anesthesia*.[38] Recognition of the importance of hand washing and the discovery of anesthetics were essential findings of the 19th century that were critical for the development of modern surgery.

The work of Holmes and Semmelweis on the importance of hand washing also opened the door for Pasteur's work on the germ basis of infectious diseases. Louis Pasteur (1822–1895) was perhaps the most outstanding clinical investigator of the 19th century (Fig. 1-10). He was trained in chemistry. His fundamental work in chemistry led to the discovery of levo and dextro isomers. He then studied the ferments of microorganisms, which eventually led him to study the detrimental causes of three major industries in France: wine, silk, and wool. Pasteur discovered the germ basis of fermentation, which formed the basis of the germ theory of disease.[39] He discovered *Staphylococcus pyogenes* as a cause of boils and the role of *Streptococcus pyogenes* in puerperal septicemia. In other studies, he carried forward Jenner's work on vaccination and developed approaches to vaccine development using attenuation of a virus for hydrophobia (rabies) and inactivation of a bacterium for anthrax.

The work of Pasteur was complemented by the studies of Robert Koch (1843–1910), who made critical technical advances in bacteriology. Koch was the first to use agar as a culture media and he introduced the petri dish, pour plates, and blood agar to make bacterial culture and identification easy and widely available. Koch cultured the tubercle bacillus and identified the etiologic agent for anthrax, which was later used by Pasteur to develop a vaccine, and he established "Koch's postulates" to prove that an infectious agent causes disease (Fig. 1-11).[39]

FIGURE 1-10 Louis Pasteur. One of the remarkable facts about Pasteur was his triumph over a great physical handicap. In 1868 at age 46, just after completing his studies on wine, he had a cerebral hemorrhage. Although his mind was not affected, he was left with partial paralysis of his left side, which persisted for the remainder of his life. This photograph, taken after he was awarded the Grand Cross of the Legion of Honor in 1881, gives no hint of his infirmity. From reference 23, p. 116.

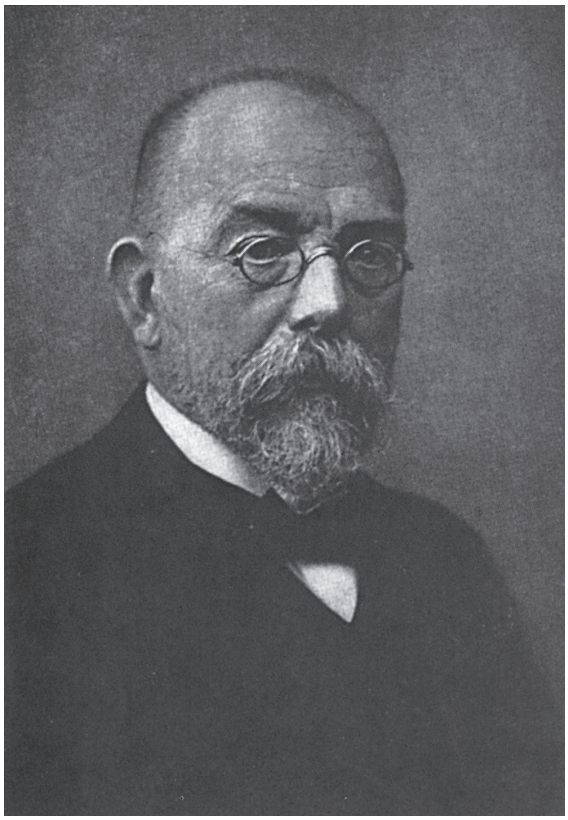

FIGURE 1-11 Robert Koch. His career in research began in 1872 when his wife gave him a microscope as a birthday present. He was then 28 years old, performing general practice in a small town in Silesia. This was an agricultural region where anthrax was common among sheep and cattle, and it was in the microscopic study of this disease in rabbits that Koch made his first great discovery of the role of anthrax bacilli in disease. From reference 23, p. 132.

The studies of Pasteur and Koch were performed during the same period as the work of the Norwegian Gerhard Armauer Hansen (1841–1912). In 1874, based on epidemiological studies in Norway, Hansen concluded that *Mycobacterium leprae* was the microorganism responsible for leprosy. Hansen's claim was not well received, and in 1880, in an attempt to prove his point, he inoculated live leprosy bacilli into humans, including nurses and patients, without first obtaining permission. One of the patients brought legal action against Hansen. The court, in one of the early cases demonstrating the importance of informed consent in clinical research, removed Hansen from his position as director of Leprosarium No. 1, where the experiments had taken place. However, Hansen retained his position as chief medical officer for leprosy[40] and later in his life received worldwide recognition for his life's work on leprosy.

In the same era, Emil von Behring (1854–1917) demonstrated in 1890 that inoculation with attenuated diphtheria toxins in one animal resulted in production of a therapeutic serum factor (antitoxin) that could be delivered to another, thus discovering antibodies and establishing a role for passive immunization. On Christmas eve of 1891, the first successful clinical use of diphtheria antitoxin occurred.[39] By 1894, diphtheria antiserum became commercially available as a result of Paul Ehrlich's work establishing methods for producing high-titer antisera. Behring's discovery of antitoxin was the beginning of humoral immunity, and in 1901 Behring received the first Nobel prize. Koch received the prize in 1905 (Fig. 1-12).

The Russian scientist Elie Metchnikoff (1845–1916) discovered the importance of phagocytosis in host defense against infection and emphasized the importance of the cellular components of host defense against infection.[41] Paul Ehrlich (1854–1915) discovered the complement system and asserted the importance of the humoral components of host defense. In 1908, Metchnikoff and Ehrlich shared the Nobel prize (Figs. 1-13 and 1-14).

At the end of the 19th century, studies of yellow fever increased the awareness of the importance of the informed consent process in clinical research. In 1897, Italian bacteriologist Giuseppe Sanarelli announced that he had discovered the bacillus for yellow fever by

FIGURE 1-12 Emil von Behring. From reference 39, p. 7.

FIGURE 1-13 Elie Metchnikoff in his forties. Reprinted frontispiece of E. Metchnikoff, *The Nature of Man: Studies in Optimistic Philosophy*. New York, Putnam, 1903. From reference 40, Figure 5.

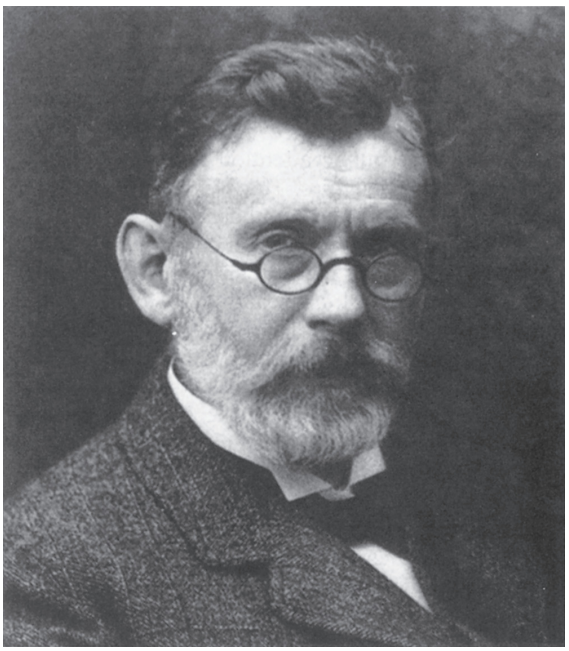

FIGURE 1-14 Paul Ehrlich. From Reference 39, p. 9.

FIGURE 1-15 Marie Curie (1867–1934).

injecting the organism into five people. William Osler was present at an 1898 meeting at which the work by Sanarelli was discussed, and Osler said, "To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain that man's sanction . . . is criminal."[42] This commentary by Osler had substantial influence on Walter Reed, who demonstrated in human volunteers that the mosquito is the vector for yellow fever. Reed adopted written agreements (contracts) with all his yellow fever subjects. In addition to obtaining signed permission from all his volunteers, Reed made certain that all published reports of yellow fever cases included the phrase "with his full consent."[42]

Toward the end of the 19th century, women began to play important roles in clinical research. Marie Curie (1867–1934) and her husband, Pierre, won the Nobel prize in physics in 1903 for their work on spontaneous radiation, and in 1911 Marie Curie won a second Nobel prize (in chemistry) for her studies in the separation of radium and description of its therapeutic properties. Marie Curie and her daughter, Irene, promoted the therapeutic use of radium during World War I (Fig. 1-15).[43]

Florence Nightingale (1820–1910), in addition to her famous work in nursing, was an accomplished mathematician who applied her mathematical expertise to dramatize the needless deaths caused by unsanitary conditions in hospitals and the need for reform (Fig. 1-16).[44]

FIGURE 1-16 Florence Nightingale (1820–1910).

7. TWENTIETH CENTURY AND BEYOND

The spectacular advances in medicine during the 20th century would never have happened without the centuries of earlier progress. In the 20th century, medical colleges became well established in Europe

and the United States. The great contributions of the United States to medicine in the 20th century are linked to the early commitment to strong medical education. The importance of clinical research as a component of the teaching of medicine was recognized in 1925 by the American medical educator Abraham Flexner, who wrote, "Research can no more be divorced from medical education than can medical education be divorced from research."[45]

Two other dominant drivers of the progress in medicine through clinical research were government investment in biomedical research and private investment in the pharmaceutical industry. These investments, closely linked with academia, resulted in enhanced translation of basic observations to the bedside. Sir Alexander Fleming's discovery of penicillin in 1928 in Scotland spawned expansion of the pharmaceutical industry with the development of antibiotics, antiviral agents, and new vaccines. Banting and Best's discovery of insulin in 1921 in Canada was followed by the discovery of multiple hormones to save lives.

In the 1920s and 1930s, Sir Ronald Aylner Fisher (1890–1962), from the United Kingdom, introduced the application of statistics and experimental design.[46] Fisher worked with farming and plant fertility to introduce the concept of randomization and analysis of variance—procedures used today throughout the world. In 1930, Torald Sollman emphasized the importance of controlled experiments with placebo and blind limbs to a study—a rebirth of the "blinded" or "masked" studies originated by Benjamin Franklin in 1784. Sollman wrote, "Apparent results must be checked by the 'blind test,' i.e., another remedy or a placebo, without the knowledge of the observer, if possible." (Fig. 1-17)[47]

With these approaches many new drugs for treatment of hypertension, cardiovascular disease, manic depression, and epilepsy, to name a few, were developed.

The spectacular advances in the 20th century were associated with troubling events in clinical research that heightened public attention and formalized the field of clinical bioethics. The Nazi's human experimentation led to the "Nuremberg Code" in 1947 that was designed to protect human subjects by ensuring voluntary consent of the human subject and that the anticipated result of the research must justify the performance of the research. The Tuskegee syphilis experiments initiated in the 1930s and continued until 1972 in African American men and the Willowbrook hepatitis studies in the mid-1950s in children with Down syndrome highlighted the need to establish strict rules to protect research patients.

FIGURE 1-17 Testing puddings and gelatins at Consumers Union. Copyright 1945 by Consumers Union of U.S., Inc., Yonkers, NY. Reprinted with permission from the April 1945 issue of *Consumer Reports*.

In 1953, the U.S. National Institutes of Health (NIH) issued "Guiding Principles in Medical Research Involving Humans" that required prior review by medical committee of all human research to be conducted at the newly opened NIH Clinical Center. In 1962, the Kefauver-Harris amendments to the Food and Drug Act stipulated subjects be told if a drug is being used for investigational purposes, and subject consent must be obtained. In 1964, the World Medical Assembly adopted the "Declaration of Helsinki" stressing the importance of assessing risks and determining that the risks are outweighed by the potential benefits of research. In 1966, Henry Beecher pointed out major ethical issues in clinical research.[48] During the same year, the U.S. Surgeon General issued a memo to the heads of institutions conducting research with Public Health Service grants requiring prior review of all clinical research. The purpose was to ensure protection of research subjects, assess the appropriateness of the methods employed, obtain informed consent, and review the risks and benefits of the research; thus institutional review boards were established. In 1967, the Food and Drug Administration added the requirement that all new drug sponsors obtain informed consent for use of investigational drugs in humans.

In the past 50 years, clinical research has become big business. The pharmaceutical industry and the biotechnology industries have engaged university-based clinical investigators in the business of clinical research. Interaction between federal investigators and industry, encouraged by the U.S. Congress when it passed the

Federal Technology Transfer Act in 1986, successfully increased the translation of basic research to the bedside by government scientists. At the same time, however, the relationship between industry and academia grew closer and new ethical, legal, and social issues evolved. Clinical investigators became increasingly associated with real and perceived conflicts. Examples of these issues included promoting an investigator's financial or career goals while protecting the patient, protecting "unborn children" while pursuing the potential use of embryonic stem cells to rebuild damaged organs, and protecting patient confidentiality as a result of gene sequencing. As a result of these issues, the public engaged in debate about the safety of current and future generations of patients who volunteer to partner with the clinical investigator on protocols.

The opportunities for doing clinical research in the 21st century are greater than ever. Today, understanding and meeting public concern are as important for the clinical investigator as performing the clinical study. Principles for conducting clinical research have evolved from centuries of experience. As the science moves forward, ethical, legal, and social issues pose special challenges for the clinical investigator. These challenges are the focus of the following chapters of this book.

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