THE OUTSTRETCHED HAND
Modern Medical Discoveries

By

Moira D. Reynolds

Preface

Selecting the material for this book has been rather difficult. According to William McNeill, an American historian, it was only after around 1850 that the practice of medicine and the organization of medical services began to make large-scale differences in human survival rates and population growth. It is this period—roughly 1850 to the present—that I have concentrated on. I have tried to be as accurate as possible, using only sources that are generally considered reliable.

The events chosen of course reflect my bias, working within the stated time frame. One hundred years from now, some of these events may have very different significance. But regardless of the importance of the selected material, I hope that the reader may gain some feeling for medical research and at the same time realize how progress in medicine also depends on the times.

I wish to thank my husband, Orland, and our son, Ronald, for making many suggestions; also Mary Frey for doing the line drawings. A special word of appreciation goes to the staff of the Peter White Library, who never failed to come to my rescue.

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CHAPTER I

The Art Is a Science—Medical Discoveries and the Scientific Method

> The greatest derangement of the mind is to believe in something because one wishes it.
>
> Louis Pasteur—1876

How do scientific discoveries come about? Some may happen by design—through carefully planned and carried out experiment; others happen by chance. Pasteur emphasized that chance favors the prepared mind; Fleming said the unprepared mind cannot see the outstretched hand of opportunity.

Throughout history there have been instances of discoveries that were rejected or remained unnoticed, later to be rediscovered by others. Sometimes a correct hypothesis was advanced, but, because of the state of the art at the time, proof was not possible.

It has happened more than once that the same discovery was made independently by two people at approximately the same time. This is understandable, for when certain facts are established or certain technology is available (the state of the art), the same approach or solution to a given problem is likely to occur to more than one person familiar with that problem. In fact, an important reason for the speed and secrecy associated with the atom bomb project of World War II was fear that German scientists might develop such a bomb before American scientists did.

Although a given discovery is usually credited to some specific person or persons, those persons have benefited from the cumulative knowledge related to the discovery. Sir Isaac Newton is reported to have said:

> If I have seen further than other men, it is because I stood on the shoulders of giants.

The Scientific Method

Science uses observation, induction, deduction, and verification to reach conclusions. Let us suppose that what is thought to be a good mode of treatment is discovered—that drug x is claimed to cure disease y. The modern scientist will ask what would happen if disease y were allowed to run its natural course without treatment. Such knowledge is referred to as the natural history of untreated disease, and it is very important in making evaluations of various types of intervention in the progress of disease. At present it is sometimes difficult to find persons who have received no treatment for an ailment; this is often the case among patients with cancer, because surgery is performed or radiation therapy or other treatment started as soon as possible after diagnosis. Some data on the natural history of untreated breast cancer is presented here. It is interesting because it is old yet compares well with three similar studies made more recently.

In 1791 John Howard, a London surgeon, and Samuel Whitbread, owner of a well-known British brewery, founded a Cancer Charity at London's Middlesex Hospital. The idea was Whitbread's, and he furnished the money. Howard made the regulations, stipulating that patients would be admitted to "remain an unlimited time, until either relieved by art, or relieved by death." He noted that under these circumstances the natural history of cancer could be studied, and he underscored the importance of keeping well-written clinical records. Figure 1 shows the pattern of survival of 250 women with untreated breast cancer, admitted to Middlesex Hospital from 1805 to 1933. Almost half of the patients were alive 3 years after the onset of symptoms, and 4 percent at 10 years. Nine patients lived 10 years or longer, and it was not until the 19th year that all had died. The solid line denoting natural survival for women of comparable ages is based on statistics for the years 1859–1934. The Middlesex results and others that followed are valuable in appraising new modes of therapy for breast cancer. It is very important to note that the data given here is concerned only with survival; it does not take into account the quality of life for the untreated patients.

A physician named Pierre Louis once studied patients at the Charité, a hospital in Paris. He divided some with pneumonia into two groups—those treated by bloodletting and those who were not bled. He came to the conclusion that bloodletting had no beneficial effect upon the course of pneumonia. His results were published in 1835 and foreshadowed the type of statistical study done today.

The Federal Drug Administration now approves drugs for general

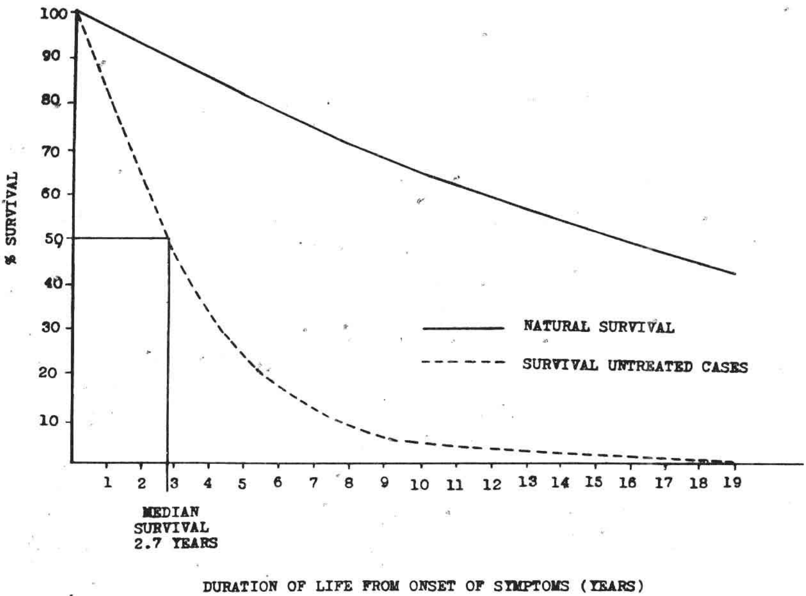

Fig. 1. *Survival of cases of untreated breast cancer. Middlesex Hospital. 1805–1933. 250 cases. (From Bloom, Ann.* N.Y. Acac. Sci. 114, *749, 1964.*)

use only after controlled clinical trials. A new drug proposed for human use has undergone extensive testing in the laboratory and on animals before clinical trials are permitted. In the course of such a trial, a drug is evaluated in three phases. In the first, volunteers are used and observed for gross toxic effects. Information about absorption, metabolism, and excretion is obtained. In Phase 2 a limited number of patients with the condition in question are given the drug. A control group of similar patients receive a placebo, or inert substance, in a container identical to the one for the drug under investigation. To minimize bias and subjective responses, it is best that subjects and investigators do not know who is receiving drug and who is receiving placebo. Such studies are called double-blind. The results of the two groups are subjected to statistical analyses to determine whether or not the new drug has a significant effect on the course of the disease. In the third phase, large numbers of patients are treated as in Phase 2. By the time Phase 3 is completed a great deal will be known about the effects of the drug. Since 1962 patients and healthy persons who participate in clinical trials must first give what is known as informed consent—consent with knowledge of the risks involved.

Ideally, new medical and surgical procedures should be subjected to clinical trials similar to those for new drugs. However, many treatments in current use have not undergone systematic clinical trials, nor are they likely to become candidates. If sufficient reliable data are available, however, it is sometimes possible to make valid comparisons between two or more modes of therapy.

Quackery

In direct opposition to the scientific method is quackery.[1] When the quack wants to promote a so-called cure or a particular method of intervention or prevention for a disease, he is likely to do it through advertising and the popular press. Reputable physicians and scientists submit their research to recognized professional journals for publication. It is judged by specialists who use rigid criteria in evaluation, and rejected if certain standards have not been adhered to. In this way worthwhile discoveries are quickly communicated to the people who can best use them. In addition, quacks tend to share some common characteristics:

- They often work in isolation, away from established medical or scientific circles.
- They are inclined to claim that organized medicine is prejudiced against their efforts.
- Their method may be "secret"—that is, not fully disclosed, with the result that it is not possible for qualified people to reproduce or evaluate it.
- Their medical records are seldom available for scrutiny; data on patients tends to be anecdotal, or the patients themselves "testify" about their cures.
- Some quacks claim that their diet, machine, injection, or whatever they seek to further has multiple benefits. To illustrate, a drug may be represented as a cure for cancer, arthritis, and allergy.
- Almost always, they refuse to submit data for statistical study.

We should emphasize that since clinical research involves human beings, it presents problems not encountered in test tube or in animal

[1] The Fraud Division of the American Medical Association, 535 North Dearborn Street, Chicago, IL 60610, supplies pamphlets and information on all types of medical fraud and misconceptions.

research. For this reason, results are often not clear-cut. When a new therapy is found, sometimes neither doctor nor patient can know whether that mode of treatment is better than an established mode or even no treatment. If the disease is life-threatening, there may be no opportunity to try another therapy should the first fail. Side effects, which may be severe, must be taken into consideration. With some types of cancer, the problem is complicated by the fact that many years must pass before any definite conclusions can be reached.

As you read on, you will see that the practice of medicine has become more scientific with the passage of time. Enormous progress has been made during the past hundred years. No doubt more marvels will be seen during the next hundred, making what seems advanced today crude indeed.

CHAPTER II

The Infinitely Small—Microorganisms as Causative Agents of Disease

If it is terrifying to think that life may be at the mercy of the multiplication of these infinitesimally small creatures, it is also consoling to hope that Science will not always remain powerless before such enemies.

Louis Pasteur

Today even a first-grader knows something about "germs," or microbes. Later he learns that man is in close contact with a variety of living organisms, too small to be seen without the aid of powerful optical devices. Some of these microorganisms are harmful, but many are beneficial.[1] Most of the microorganisms that produce human diseases fall into the following groups:

Bacteria

These are one-celled plants without chlorophyll. Cells that are spheres are called *cocci*, straight rods are called *bacilli*, and curved rods are called *spirilla*. In the laboratory, a bacterium will multiply in liquid or on solid medium if its specific nutritive requirements are met and if there is proper control of such factors as temperature, the degree of acidity, and the oxygen tension. If pus from an abscess, for example, is streaked on a suitable bacteriologic medium (which usually contains agar-agar, to give it the consistency of stiff Jell-O), which is then maintained at body temperature in a thermostated incubator, within 24 hours each single organism present in the pus will have multiplied (by dividing into two parts; each of the two parts in turn dividing into two parts, etc.) to form what is called a colony, visible to the eye.

[1] A fungus caused the terrible potato famine in Ireland in the 19th century. A fungus also gave us penicillin.

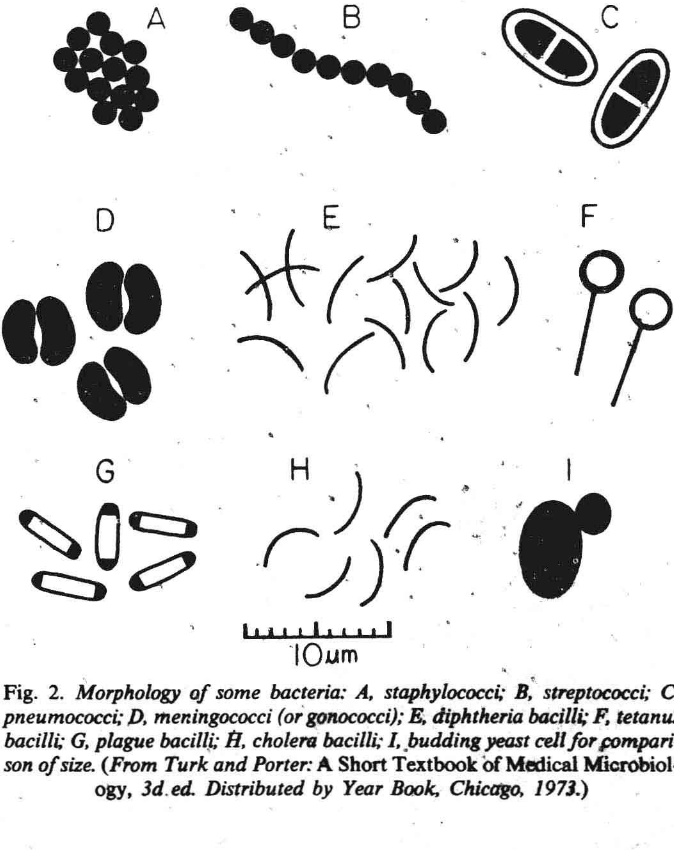

Fig. 2. *Morphology of some bacteria: A, staphylococci; B, streptococci; C, pneumococci; D, meningococci (or gonococci); E, diphtheria bacilli; F, tetanus bacilli; G, plague bacilli; H, cholera bacilli; I, budding yeast cell for comparison of size.* (*From Turk and Porter:* A Short Textbook of Medical Microbiology, *3d ed. Distributed by Year Book, Chicago, 1973.*)

This colony, composed of millions of descendants of the original bacterium, has a characteristic appearance on any given medium. The shape of the individual bacterium, as seen microscopically, and its growth characteristics and colony appearance help to identify it. In addition to classification of a bacterium by its physical characteristics, many biochemical tests are also used. Some pathogenic bacteria may cause specific diseases such as tuberculosis and gonorrhea, and some cause a variety of less specific conditions, such as boils.

Fungi

This group is somewhat similar to the bacteria, but there are differences in microscopic appearance and growth characteristics—particularly the ability to grow well at room temperature. Some pathogenic fungi can cause skin

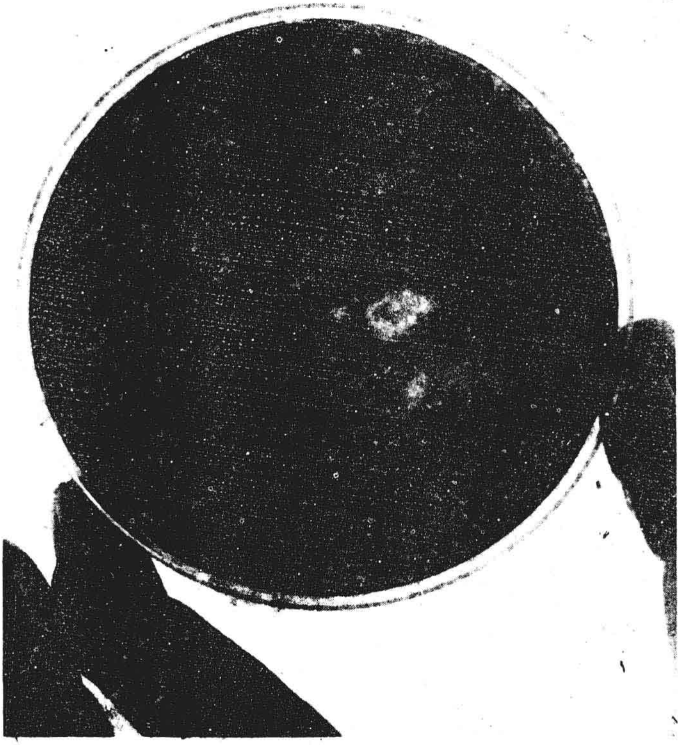

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Fig. 3. *Bacterial colonies growing on solid medium.*

infections as well as other mild afflictions, and some can cause serious systemic disease.

Rickettsiae

These organisms are smaller than bacteria. They do not grow on the media used for bacteria, since they must be inside a living cell before they can multiply. They are intestinal parasites of bloodsuckers such as ticks, mites, rat fleas, and lice. Rickettsial infections in man include typhus, Rocky Mountain spotted fever, and Q fever.

Viruses

Most viruses are too small to be seen with the ordinary light microscope but are visible with the electron microscope. Like the rickettsiae, they grow only within living cells. Viruses comprise a large and heterogenous group. Familiar viral diseases are mumps, influenza, and hepatitis.

Protozoa

These are one-celled animals—most of them larger than bacteria. Protozoan diseases include malaria, trypanosomiasis, and amebic dysentery.

Because microorganisms cannot be seen by the naked eye, it was relatively late in human history before they were recognized as causative, or etiologic, agents of disease. We know that epidemics of bubonic plague (the Black Death), cholera, and other infections occurred, causing great fear and untold havoc. Sometimes the contagious nature was recognized, as evidenced by the fact that the first quarantine of ships took place in Venice in 1377. It was an attempt to prevent the spread of plague. There were varied explanations about the cause(s) of this, all erroneous. To illustrate, 2,000 Jews were hanged in Strassburg because it was felt they were responsible for the pestilence. Then in the summer of 1665, when the disease destroyed one-fifth of London's population, dogs were considered the cause. The true culprit was the rat, which carried *Yersinia pestis,* the bacterium that causes plague.

In his *De Contagione,* published in 1546, the Italian physician-poet Girolamo Fracastoro stated correctly that diseases could be spread by direct contact between persons, by inanimate objects, or through the air. It would be almost fifty years until the invention of the microscope, with which the infecting agents could be seen, so Fracastoro had no proof to back his claims.

Suggestions that "wonderfully minute creatures" might cause certain diseases became more frequent. Two examples follow. In 1762 Marcus Plenciz of Vienna, a physician, advanced the belief that specific forms of living agents caused specific diseases. By 1835 Agostimo Bassi of Piedmont had proved that a blight affecting silkworm larvae was caused by a fungus, and in his 1844 publication on contagion he stated that "smallpox, spotted fever (typhus), bubonic plague, and syphilis are caused by living parasites, animal or vegetable." So we see that many centuries of speculation and even investigation preceded the work of Louis Pasteur (1822–95), which put the germ theory of disease on a firm basis.

Louis Pasteur was born in France, the son of a former sergeant in Napoleon's army, who owned a small tannery. Louis was trained in physical science, not medicine. His first investigations concerned the isomers of tartaric acid. A recognized crystallographer had claimed that two forms of tartrate had identical composition, although one turned the plane of polarized light to the right and the other remained inactive. Pasteur recognized an incompatibility in these findings and proceeded to demonstrate it. He evaporated a salt of the inactive acid to obtain crystals. He noticed that these crystals were of two forms. With painstaking care he separated them and found that one was a

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Fig. 4. *Louis Pasteur (1822–95).*

mirror image of the other. In solution, the optical activity of one neutralized the activity of the other.

You may wonder about the relation of tartaric acid to medicine. There is none, in the direct sense. But this piece of work shows unusual investigative ability and was the forerunner of many more brilliant investigations. Throughout his professional life Pasteur showed keen observation; he had superb intuition; he made excellent deductions, and he had great talent in designing and executing reproducible experiments that would prove (or disprove) a hypothesis. He worked indefatigably and was not deterred by an attack of paralysis (left hemiplegia) suffered at the age of 46.

In 1855 he began to study fermentation, using equipment paid for by himself. Two years later he presented his conclusion that the conversion of sugar to alcohol and carbon dioxide was due to yeast activity and introduced his belief that every transformation of organic matter is caused by a specific species of microorganism. (We should note here that the actual chemical reactions are catalyzed by *enzymes* produced by living organisms such as yeast and bacteria.)

Since antiquity there had been widespread belief that life could arise spontaneously from nonliving material—for instance, when maggots appeared in rotting meat, it was held that they arose spontaneously. Maggots can be seen, but when the agents of putrefaction and other processes were microscopic, the situation was naturally still more perplexing. From time to time the idea of spontaneous generation had been questioned or refuted by thoughtful men, but it was Pasteur who showed by experiments that a given organism comes only from preexisting organisms of the same species, frequently present in the air. Pasteur was introduced to the problems of infectious disease when he investigated the silkworm diseases that threatened to ruin the French silk industry. His understanding of fermentation led him to suggest a process of partial sterilization, applicable to wine, beer, vinegar, milk, and other beverages as well as food products. Pasteurization, as it is now known, usually consists of subjecting the material to 60 to 66° Celsius (abbreviated C) for 30 minutes. This causes a marked reduction in bacterial activity without seriously changing taste.

But from the standpoint of medicine, Pasteur's most important contribution by far was the discovery that specific infectious diseases are produced in the host by the multiplication of specific microorganisms. Armed with culture flasks and sterile pipettes, he and his assistants visited hospital wards and morgues. Working with various veterinary and human maladies (of the latter, hospital gangrene, septicemia, childbirth fever), he carefully isolated causative agents and studied them. As he became more familiar with the organisms, he learned how to attenuate some, so that their virulence was lost. He had great interest in the body's response to the agents of disease and surmised correctly that the attenuated material could evoke an immune response without causing the disease. He made successful vaccines for chicken cholera (by aging the culture of the bacillus), for anthrax in cattle and sheep (by cultivation of this spore-forming bacillus at 42–43° C), and for swine erysipelas (by passage of the bacterium through rabbits). And his name will be forever associated with the prevention of rabies.

We know now that human rabies is transmitted by a bite from an infected dog or other animal whose saliva contains the virus responsible. After the virus reaches the brain, it multiplies, causing extensive damage. It then travels to the salivary glands and other parts of the body. Rabies, sometimes called hydrophobia, is incurable and fatal once it is established. It is characterized by a violent and painful spasm of the throat when swallowing is attempted, causing the victim to fear drinking (hence the name).

Pasteur had discovered that whatever caused rabies did not grow in the broth he used for most bacteria; also, he could not see the microorganism with his microscope, but he felt certain that the saliva from a rabid dog contained agents capable of transmitting the disease. (In 1885 he said, "One is tempted to believe there is a microorganism infinitely small.") He succeeded in modifying the virulence of the virus by drying infected spinal cords of rabbits. Because the incubation period of rabies is usually at least a month, he reasoned that emulsions of the cord (a vaccine) could be injected daily until immunity to rabies was achieved. Each injection contained less attenuated and therefore more virulent material. He found that this method established immunity in dogs in 15 days.

In 1885 a nine-year-old named Joseph Meister was brought to Pasteur for treatment. The boy was so seriously bitten by a rabid dog that it seemed inevitable he would develop rabies, so Pasteur decided to try this method, not yet used on a human. The decision brought criticism from his foes and even from a close colleague. Joseph received an injection of infected rabbit cord, dried for 14 days. Then he was given 12 successive inoculations of increasingly virulent material over a 9-day period. He did not develop the disease. In later years Joseph Meister became gatekeeper of the Pasteur Institute in Paris, erected in 1888 and dedicated to research in the preventive treatment of infection. He committed suicide in 1940 during the Nazi invasion of France.

Up to 1935 more than 51,000 persons had been inoculated to prevent rabies, with a mortality of only 0.29 percent. The efficacy of the rabies vaccine has always been questioned because it is not known how many of the inoculated persons would have developed rabies otherwise. The vaccine in current use is grown in embryonated duck eggs and inactivated with a chemical. The broader importance of Pasteur's work with rabies vaccine is that it paved the way for immunization to yellow fever, another viral disease, far more widespread than rabies. The success of the veterinary vaccines demonstrated clearly that vaccines have potential in human medicine. Thus Pasteur may be regarded as the founder of the science of immunology.