Public Health Reports. (1980). *Landmarks in American epidemiology, 95*(2). Special issue.
Stallones, R. A. (1980). To advance epidemiology. *Annual Review of Public Health, 1,* 69–82.

PART I

Background to Epidemiology

To those who say, "How can we admit the possibility of infection while the religious law denies it," we reply that the existence of contagion is established by experience, investigation, the evidence of the senses and trustworthy reports. These facts constitute a sound argument. The fact of infection becomes clear to the investigator who notices how he who establishes contact with the afflicted gets the disease, whereas he who is not in contact remains safe, and how transmission is effected through garments, vessels and earrings.

— *Ibn-al-Khatib, 14th-century Moorish scholar*

To understand any contemporary science it is necessary to have some understanding of its roots. Chapter 1 provides a historical overview of changing concepts of the causation of disease. Epidemiologic methods originally developed in an attempt to compensate for the failures of germ theory in the explanation of infectious disease. Gradually, epidemiologic theory grew from the infectious disease oriented model of classic epidemiologic theory (Chapter 2). Today, epidemiology provides a theoretical framework for health service, including disease prevention and health promotion.

CHAPTER 1

Mankind's Changing Concepts of Disease

It is the purpose of this chapter to provide the reader with an introduction to the variety of ways in which our ancestors attempted to explain the causes of disease. A historical perspective such as this can provide a valuable insight into many current beliefs about health and disease. It is hoped that such a perspective will also inspire some humility regarding our own certainties as we examine the false conceptions that have been accepted in the past.

Such a brief history of the concepts of disease necessarily omits a great deal. The reader should be aware that theories of disease causation were not replaced by others in a neat and orderly progression. Instead, they frequently overlapped and coexisted. Today, we still view the elements of these theories in popular ideas about disease and in the practice of medicine.

Primitive Peoples' Concepts of Disease

Early man attributed disease to the actions of evil spirits or ghosts. Alternately, it was believed that disease could be the result of witchcraft—a curse or an "evil eye" put on the disease victim by an enemy. Disease, like famine, drought, or lightning, was believed to be an act of the supernatural, beyond human control or human understanding.

To prevent disease, one made sacrifices to the gods, obeyed the taboos, and avoided haunted places. Charms and spells were also used to protect one from disease. These primitive notions still exist to some extent today. In the midst of our modern cities, one can still find those who by charms, amulets, and potions will guarantee to prevent or cure disease, to bring you your true love, or to give you luck at gambling.

The Hippocratic–Galenic Theory

The First Epidemiologist

The Greek Physician Hippocrates of Cos, who lived from about 460 B.C. until about 377 B.C., was the earliest known authority to attempt to explain disease on a rational basis. Because Hippocrates treated disease as a mass phenomenon as well as an individual occurrence, he has been called the "first epidemiologist." One of his most noteworthy contributions is the distinction between "endemic" diseases, which vary in prevalence from place to place, and "epidemic" diseases, which vary in prevalence over time. Hippocrates' writings are also the earliest in which there is a systematic attempt to relate the occurrence of disease to environmental factors. These relationships are examined in three of the books attributed to Hippocrates—*Epidemic I, Epidemic III*, and *On Airs, Waters and Places.*

Hippocrates' greatest contribution to epidemiology is one of approach. He carefully observed and recorded associations between certain diseases and such factors as geography, climate, diet, and living conditions. Lacking the statistical concepts so vital to modern epidemiology, he was only able to assess these observations intuitively. From a framework of observations, he built a theory of disease causation that was consistent with the philosophy of nature held by the leading Greek philosophers of his day.

The philosophy held that everything was composed of different combinations of particles that individually were too small to be seen. The hypothetical particles were known as "atoms." For this reason it was known as the *atomic theory*—a rather modern sounding term. However, unlike our modern atomic theory that identifies many different atoms, the ancient Greek atomic theory assumed only four kinds of atoms. There were atoms of earth, of air, of fire, and of water. Each atom possessed two of the four irreducible qualities of wetness, dryness, warmth, and coldness. Earth was cold and dry; air was hot and wet; water was cold and wet; and fire was hot and dry.

Hippocrates taught that the human body was composed of four substances, which he called the four "humours"—blood, phlegm, yellow bile, and black bile. Each humour was made up of one type of atom. Thus, blood was made up of air and possessed the properties of being hot and wet. Likewise, phlegm was made up of water, yellow bile of fire, and black bile of earth. In health these four humours were in balance, with the body containing equal parts of each.

Consistent with the value that ancient Greek philosophers placed on moderation and balance, Hippocrates taught that illness resulted when an imbalance occurred in the humours. An excess of hot/wet blood, for instance, could produce fever, sweating, and diarrhea, while an excess of cold/dry black bile could cause chills and constipation.

In part, such an imbalance might be the result of diet. Spicy hot foods would stimulate the production of more of the hot humours—yellow bile or blood. Other foods might possess the properties of being cold, of being dry, or of being wet, and thus would stimulate the production of the humours with those properties. Some of the writings attributed to Hippocrates seem to place great emphasis on diet as a cause of disease, although others deny this possibility, giving diet a role in treatment but not in causation of disease.

More important than diet in Hippocrates' view was the influence of constitution. The term *constitution* is in some ways synonymous with environment. It includes such obvious environmental factors as climate and major geographic features of the area (rivers, swamps, mountains). It also includes astrological influences and the influence of comets and meteors. The fiery trail of a comet or meteor was seen as obviously putting excess fire into the atmosphere, which could cause an epidemic of a yellow bile disease.

Hippocrates' approaches to treatment attempted to restore balance. Colds and other conditions associated with cold/wet phlegm were treated with hot spicy foods and applications of mustard or other irritants to the chest to produce a sensation of warmth. Fevers were treated by abstaining from food that might carry hot/wet air or hot/dry fire. There also were efforts to remove the excess humours. Excess blood was removed with leeches, by "cupping" (in which blood was drawn from cuts with a vacuum) or by simply opening a vein (or, sometimes, with disastrous results, an artery, as the distinction between veins and arteries was not yet known). Excess phlegm or black bile was sweated out in a steam bath or was eliminated by vomiting. Excess yellow bile or black bile was eliminated by high (or colonic) enemas.

Hippocrates still has a place in medical education. The Hippocratic Oath is, of course, both a medical tradition and a basis for medical ethics. As "the father of medicine," as well as "the first epidemiologist," Hippocrates is an important historical figure in the study of medicine. As recently as the first quarter of this century, however, the Hippocratic theory was still being taught in American medical schools not as history but as a valid theory of disease causation.

A great many elements of the Hippocratic theory have become a part of our common cultural heritage and thus of the way most of us think about disease. For instance, the widespread myth that chills and wet feet cause the common cold has its roots in the Hippocratic view that colds are due to an excess of phlegm (made up of the elements of earth and water). Likewise, the old saying, "Feed a cold and starve a fever," was a precept of Hippocratic medicine. In Puerto Rico and in New York City you can find traditional healers who practice "hot and cold therapy," a dietary therapy that is almost pure Hippocratic medicine. In many ways the Hippocratic tradition is still very much alive. Bloodletting remained a common medical practice until the late nineteenth century, colonic enemas continued to be a part of many physicians' practice in the early part of this century, and are still featured in many alternative health-care programs.

Hippocrates Revisited and Revised

The theories of Hippocrates were elaborated on more than half-a-century later by the Roman physician Galen. Born in the city of Pergamum in Asia Minor around 130 A.D., Galen began the study of medicine at an early age. At the age of 20 he began a sort of itinerant practice of medicine, wandering from place to place, apparently with no lasting professional or financial success. Eventually he became an army physician, which led to his becoming personal physician to the emperor Marcus Aurelius in 169 A.D. This privileged position allowed him ample time for research and writing. His literary output during this period was enormous. Although many of his manuscripts were destroyed in the year 192 and many more were lost over the ages since then, the texts that have survived amount to more than 90,000 words.

Galen's studies included the fields of anatomy and physiology, as well as theories of disease causation. His contributions to the field of physiology earned him the title "father of experimental physiology," while his writings on anatomy remained the accepted standard for 13 centuries. The dissection of human bodies, however, was as unacceptable a practice among the Romans as it was among the Greeks before them. Galen based his ideas of anatomy on what he had seen of wounded men in the army and in the gladiatorial arena, and on the dissection of animals — of the pig, the ape, the dog, and the ox. His anatomy showed the human breastbone to be segmented like that of an ape, the liver divided into many lobes like that of a hog, the uterus shaped in two long horns like that of a dog, the hip bones flared like those of an ox, and so on.

The manner in which he made his contributions to the understanding of disease causation made him the first "armchair epidemiologist." That is, he based his theories on the observations of others (especially of Hippocrates) rather than going out to make his own observations. Thus, his theory is basically an elaboration on Hippocrates' teachings.

In order to explain why some people become ill while others exposed to the same "constitution" do not, Galen added two new elements to Hippocrates' theory of the four humours and the constitution. These two new elements were knowm as *temperament* and *procatartic factors*. Procatartic factors referred to the influence of a person's way of life on the types of diseases from which he was likely to suffer. Slaves suffered from diseases quite different from those afflicting nobles; the disease experiences of merchants were quite different from those of soldiers or fishermen or farmers. In modern terms we might call these lifestyle factors or, even more appropriately, occupational factors.

In his concept of temperament, Galen disagreed with Hippocrates' teaching that human bodies are naturally composed of equal parts of the four humours. Instead he believed that in each person one humour predominated. This predominance of one humour or another was known as temperament. Of course, already being overendowed with one of the humours made the person especially vulnerable to the diseases associated with that humour.

An excess of each of the humours was associated not only with a particular disease vulnerability but also with a particular personality type. Persons with an inborn excess of blood, for instance, were said to have a sanguine temperament, characterized by a cheerful manner and optimistic outlook. The sanguine individual also possessed a typical appearance, with a robust red face and often with red hair as well—the blood showing through. Likewise, the phlegmatic person, oversupplied with cold watery phlegm, was passive and unexcitable, with dull, unexpressive features. An excess of black bile produced a melancholic temperament, prone to sadness and depression, and a thin, pale appearance. Yellow bile in excess produced a choleric personality that was easily aroused to anger—a hot temper and dry irritability from all that hot/dry fire in the yellow bile.

The Concept of Miasma

With the rise of Christianity the teaching of pagans such as Galen fell for a time into disfavor. Throughout most of Europe, demonic possession once again became the accepted explanation for all illnesses. The writings of many of the classic philosophers and scholars, including Galen, were preserved by Arab scholars following the rise of Christianity and the fall of the Roman Empire. Eventually, many of these "pagan" writings were reinterpreted by Christian scholars as part of the growing Christian theology, and were accepted by the Catholic Church. The accepted version of the writings of such pagans as Aristotle and Galen came to have almost scriptural authority.

The Hippocratic–Galenic theory as it survived into this era was far simpler and less sophisticated than its original sources. A complex theory was no competition for the demonic possession theory of disease with which it was to coexist for centuries. Influences such as climate and lifestyle were largely forgotten while the importance of comets and meteors as causes of epidemics remained prominent. Later physicians began to speak of "miasmas"—vapors rising from rotting refuse or stagnant water. These miasmas were seen as the means by which diseases were spread. When people breathed miasmas their humours were affected resulting in disease.

Preventive measures were centered on covering up or eliminating the miasmas. One slept with the windows closed in order to keep the night air out because it was believed that night air was particularly prone to carry miasmas (and also because demons were more likely to prowl at night). Herbs and incense were used to perfume the air, and to fill the nose and crowd out any miasmas. It was also believed that miasmas could be settled out of the air by loud noises; so that bells, gongs, and cannon fire were widely used as antiepidemic measures.

The miasma concept continues to dominate a great deal of popular thought about disease. As recently as two generations ago, many Americans wore asofoctida (or asofidity) bags around their necks in the winter to prevent colds and the flu (the bags contained asofetida and other pungent-smelling herbs). During World War II many allied military hospitals still burned incense to prevent infections. Today the public still spends money on camphor and menthol chest rubs, and on vapor-action cough drops.

Germ Theory

The successor to the Hippocratic–Galenic theory was the germ theory. The idea that living organisms might cause disease had been considered by physicians at least as far back as ancient Rome. Lucretius, Varro, and Columella all speculated on this possibility, but it wasn't until centuries later that Fracastorius developed a theory of disease based on this idea, and it was only in the late 19th century that it gained wide acceptance.

Fracastorius and the Concept of Contagion

Tradition holds that among the wonders of the New World brought back to Europe by Christopher Columbus, or at least by some of the seamen under his command, was a new disease. Faced with this new disease, the people of every European nation seemed compelled to blame the disease on another nation. The French called it "the Italian disease," the Poles called it "the disease of the Germans," the Russians called it "the Polish disease," and the English and the Italians called it "the French disease." One of the popularizers of the last of these nicknames was the 16th-century Italian physician and poet Hieronymus Fracastorius (1478–1553), author of the poem "Syphilidis, sive Morbi Gallici." In poetical form this work gave the disease its formal name syphilis and summarized the then current state of knowledge regarding the disease, its symptoms, and its treatment. It did this in the guise of a fable about a herdsman named Syphilos, who was the first victim of the disease, inflicted on him as punishment for blasphemy when he cursed the sun god for causing a drought that was killing his animals.

> He first wore buboes dreadful to the sight,
> First felt strange pains and sleepless past the night,
> From him the malady received its name.
>
> — *Fracastorius, Syphilidis, sive Morbi Gallici.*

Fracastorius was apparently a pen name, in latinized form, for Girolamo Fracastoro (or Fracastor), who practiced medicine in the Italian city-state of Verona. Apparently a very persuasive man, Fracastorius was able to popularize through his writings and personal contacts a radical new view of disease causation.

His theory was put forth in 1546 in a book entitled *De Res Contagiosa.* His theory was that disease was transferred from one person who has the disease to another person who then develops the disease. He called this transference *contagion* and argued that it occurred through the conveyance of disease by tiny imperceptible particles, which he called *seminaria contagium*—seeds (or germs) of contagion.

Fracastorius distinguished three types of contagion. The basic type was spread by direct contact only. In the second type, the germs of contagion were conveyed person-to-person by what he called fomes—"clothing, wooden objects, and things of that sort, which though not themselves corrupted, can, nevertheless, preserve the original germs of the contagion and infect by means of these—which a modern epidemiologist would call fomites. Thirdly, there were contagions that could infect "at a distance."

One important person who was convinced by Fracastorius of the merits of his theory was Pope Paul III. It is as a result of Pope Paul's belief in the theory of contagion that the Council of Trent was held in Bologna, Italy instead of in Trent, France (an important event in the history of the church). The presence of contagious disease in Trent (apparently syphilis among the prostitutes of Trent) was recognized by the Pope as a threat to the church leaders and so he transferred the council to Bologna where the conditions did not exist. Such support for the theory did not outlive Fracastorius. Following his death, the concept of contagion was largely forgotten for the next 200 years.

The concept of quarantine—the exclusion or isolation of persons suffering from certain diseases—was not forgotten. Although quarantine continued to be practiced, acceptance of the practice was based as much on the demonic and miasma concepts of disease as on any concept of contagion.

In the late 18th century, the English physician John Hoygarth used true epidemiologic methods in studying the spread of fever within families from the first diseased family member. From the patterns of distribution that he found, he inferred that different diseases had different incubation or latent periods during which infection is present but symptoms have not developed. In 1774 he proposed that instead of quarantining fever victims within their own homes, they should be isolated in "spacious airy, separate apartments," within a special "fever ward" of a hospital. Nine years later, he established the first such ward in the attic of the infirmary in the city of Chester. The success of the Chester "fever ward" soon led to the establishment of similar units in Manchester, Liverpool, and other cities, and gave momentum to the rise of a contagion-centered theory of disease—germ theory.

The Discovery of Microorganisms

One barrier to acceptance of the concept of contagion had been the notion of invisible particles or of living things too small to be seen. Invisible miasmas were easy enough to believe in; everyone knew that you can't see an odor. But, obviously, no one had ever seen an invisible particle or an invisible organism.

A retired Dutch drape-maker by the name of Anton van Leeuwenhoek (1632–1723) provided the answer to this objection. The writings of Galileo, banned in most of Europe, were readily available in the tiny libertarian country of Holland. Astronomy and telescopes were very much in fashion as gentlemen's hobbies in the Holland of van Leeuwenhoek's time. He was one of the first to adapt the principle of the telescope to the task of examining very small things close up instead of examining very big things far away. In brief, he invented the microscope.

Peering through his simple microscope, van Leeuwenhoek discovered tiny living things in a drop of water. These tiny organisms, which he called "animalcules," were soon recognized as the invisible living things in the contagion concept. The connection was made by some but it was not yet germ theory's day.

"Clean Hands May Carry the Disease"

Childbirth was long one of the major causes of death. The principal reason for this was puerperal fever, or childbirth fever, which struck females a few hours to a few days after giving birth to a child. High fever, weak rapid pulse, and abdominal pain often led to the death of the female. Puerperal fever became increasingly common as more women began having their babies delivered in a maternity hospital (or "lying-in hospital"). Epidemics of puerperal fever occurred in these hospitals and were blamed on miasmas associated with the weather. It is reported that in the year 1776 the weather was such that not one woman survived childbirth in the city of Lombardy.

In 1845, Oliver Wendell Holmes, a physician better known as a literary figure and father of a Supreme Court Justice, wrote a paper called "The Contagiousness of Puerperal Fever." In this paper Holmes argued that puerperal fever was an infection transmitted from one patient to another by the physician or midwife. The reaction to this radical view ranged from indifference to outrage.

In a later paper entitled "Puerperal Fever as a Private Pestilence," Holmes replied to his critics. In it he referred to the work of a physician named "Senderein," who had lessened the mortality due to the disease by washing his hands with chloride of lime. He replied to the criticisms of a Dr. Meigs, who had resented the suggestion that physicians had dirty hands, and cited the case of a Dr. Simpson who though an "eminent gentleman" (and thus presumably incapable of having dirty hands) had nevertheless had a number of cases of puerperal fever among the women he had assisted in childbirth. Holmes replied that if that was true, then "it follows that a gentleman with clean hands may carry the disease." Once the initial furor over these two papers had died down, the medical community soon forgot all about Holmes' unpleasant idea.

The "Dr. Senderein" referred to by Holmes was actually Ignaz Semmelweis (1818–1865). Semmelweis was a Hungarian who began studying law at the University of Vienna but switched to medicine and eventually specialized in, and revolutionized the field of, obstetrics. After graduation he obtained a position at the University of Vienna's maternity hospital. He was in charge of the hospital's First Division in which babies were delivered by medical students. In the Second Division midwife students delivered the babies.

Semmelweis discovered that over a 60-year period the death rate due to puerperal fever in the First Division ranged from 68 to 158 deaths per 1,000 births with an average of 99 deaths per 1,000 births. In the Second Division over the same period the death rate from puerperal fever overaged 33 per 1,000 births. It was this substantial difference between the death rates of the two populations of patients that set him to search for a cause.

Semmelweis was able to quickly dismiss such possible explanations of the difference as miasmas arising from dirty laundry or accumulating due to poor ventilation. The condition of laundry and ventilation in both divisions were equally poor. Likewise, he concluded that poor diet could not be the cause of the difference because the food was the same in both divisions.

One theory that had been proposed was that the high rate of puerperal fever was caused by embarrassment. The modesty of the women in the First Division, it was suggested, had been outraged by having male physicians care for them during childbirth. Semmelweis rejected this theory, in part because most of his patients did not seem to be particularly modest. More convincingly, he pointed out that women of the upper classes who were usually attended to by male physicians

when in labor did not experience a high rate of puerperal fever. Yet another suggestion was that the high rate was caused by fear. Women were afraid of being cared for in the First Division and this fear, it was argued, caused them to develop puerperal fever. The circularity of this logic was obvious to Semmelweis. The women were afraid of the First Division because of the high death rate, so their fears could not have caused the high death rate.

Semmelweis found that the only difference between the two divisions was who delivered the babies. He looked for differences between the ways that medical students and midwife students delivered babies and found none—they were, after all, being trained by the same teachers. The one difference (aside from sex) that he did find between the medical students and the midwife students was in the way they spent their time between deliveries. When not delivering babies, the midwife students made tea, gossiped, and knitted. Between births the medical students dissected cadavers—dead bodies.

At about the same time that Semmelweis made the above observation, one of his colleagues, Dr. Kolletschka, died. Dr. Kolletschka's finger had been cut when a student's scalpel slipped while they were dissecting a body. He died as a result of this slight wound. Semmelweis noted that the symptoms of Dr. Kolletschka's fatal illness were the same as those of puerperal fever. The two observations led him to conclude that puerperal fever was at such a high rate in the First Division because of something the medical students got on their hands while dissecting the unrefrigerated bodies. With this in mind, he ordered all of his medical students to wash their hands in a solution of chloride of lime before seeing any patients. At that time the puerperal fever death rate in the First Division was 120 per 1,000 births. In the 7 months after his hand-washing rule went into effect, the rate was 12 deaths per 1,000 births—the first time in the history of the hospital that the death rate in the First Division was lower than that in the Second. Also for the first time ever there were 2 months in which no patients in the First Division died.

This great contribution resulted in Semmelweis being suspended from his position for 6 months and, subsequently, being subjected to a variety of harassments. He left Vienna abruptly and returned to his home in Budapest, where he became head of the maternity hospital and wrote a book on his findings on puerperal fever. His theory was regarded by many of his colleagues as evidence of insanity. Eventually, he was sent back to Vienna as a mental patient. When examined at the mental hospital, it was discovered that he had a cut on his finger that had probably resulted during one of his last operations. He died of the fever he had first recognized as being same thing as puerperal fever. Unlike Fracastorius, Semmelweis' ideas did live on after him, although acceptance was slow.

"Germ Theory Achieves Dominance"

Germ theory came to be the dominant theory of disease under the leadership of Louis Pasteur (1827–1912). It is a surprise to many to discover that Pasteur was not a physician. He was in fact a chemist whose work had originally centered on the study of crystals. He had written his dissertation on two forms of tartaric acid, and this led naturally to the study of wine because tartaric acid is one of the naturally occurring substances that gives wine its flavor. Pasteur's attention was drawn to the diseases of wine—a problem of serious importance to the French economy of his time.

For centuries it had been known that if grapes were crushed the juice would naturally ferment forming alcohol and turning the grape juice into wine. No one knew how or why this natural process took place, nor why the process stopped as automatically as it started. About 15 percent of the juice would be turned into alcohol but no more. Equally, it was not known why the process went bad in diseased wine. But it was known that in some batches the juice putrified producing a bitter, ropy wine. This unpredictable sickness could wipe out a single batch or an entire vintage. The person who could prevent sick batches of wine could save the wine industry from periodic losses that were at times disastrous. If that person could learn how to get the fermentation process to continue beyond its natural limit, then that person would possess knowledge worth a fortune. Pasteur set out to be that person.

Pasteur discovered that fermentation was a result of the growth of yeast in the grape juice. The yeasts grew naturally in small amounts on the skin of the grape. When the grape was crushed the yeasts reached the sugar-rich juice and multiplied prolifically. Each of the microscopic yeast organisms consumed sugar from the juice and excreted alcohol as a waste product. Any organism's waste products are poisonous to that organism when they are in a high enough concentration. When the level of alcohol in wine rises to about 15 percent, the yeasts die off having been poisoned by the rising concentration of their own excrement. Thus Pasteur, in discovering how fermentation took place, had also learned that it could not be made to continue beyond its natural stopping point. He was able, however, to learn the cause and means of prevention for

sick wine. Diseased wine, he found, contained bacteria that had replaced the yeasts that should have reproduced in the juice. He found that this could be prevented by heating the grape juice to a temperature high enough to kill off any organisms in it but not high enough to damage the juice. This process came to be known as *pasteurization*. Once the grape juice was pasteurized the winemaker could add yeast from a good batch of wine to assure that the healthy fermentation process took place. Later, when it was learned that milk was commonly a source of infection with the germs of tuberculosis, typhoid, and other diseases, pasteurization of milk became an important public health measure.

Pasteur next turned his attention to a disease that was of major economic importance. The silk industry, one of France's leading industries at that time, was threatened by an epidemic that could have destroyed the industry. Pasteur was able to identify two separate infections that were attacking the silkworms and developed a preventive for each. Out of gratitude for his contributions to two of France's major industries, the French government provided Pasteur with a house, a laboratory, and a pension. This left Pasteur free to pursue his interests without worrying about financial support. He continued his researches into disease, studying anthrax and chicken cholera.

It was in the course of his studies of chicken cholera that Pasteur made a discovery of far-reaching significance. He had isolated the bacteria that is the agent of chicken cholera. He grew this bacteria in a broth that had to be renewed periodically or the bacteria would be poisoned by their own waste products (like the yeast in wine). Pasteur renewed his cultures of the bacteria by putting a few drops of the old broth (containing the bacteria) into the fresh broth. A few drops of this broth placed on bread and fed to a chicken invariably resulted in the chicken developing chicken cholera and dying. Through an oversight, Pasteur let some of his broth go longer than usual without being renewed. When he fed this broth to some chickens, the became sick but did not die. Furthermore, when he later fed the chickens a full-strength bacterial broth, they did not become ill. They had acquired an immunity to chicken cholera by overcoming the infection with the bacteria from the weakened culture. Thus, Pasteur had discovered the principle of *bacterial vaccination*. He was to apply this principle in developing vaccines for a number of important diseases. The greatest impact was to result from his work on rabies.

Although more common in the 19th century than today, rabies was not one of the leading causes of death at the time. It was more feared than many of the biggest killers. With other diseases there was always the possibility of recovery but rabies was always fatal. To be bitten by a rabid animal was a sure sentence of death—and an extremely painful death. No medical treatment could save the life of a rabies victim or relieve the pain.

Through a lengthy series of experiments, Pasteur was able to establish that the infectious organism for rabies was located in the nervous systems of rabid animals. He was not, however, able to isolate the organism. He could not see the organism under a microscope. He could extract the organism in a culture but when he tried to filter out the organism it passed right through the filter. As a result he called the organism a filtrable virus, a name that means a living thing able to pass through a filter.

Pasteur was able, nevertheless, to develop a vaccine for rabies. He infected rabbits with rabies and then, when they died, removed their spinal cords. He weakened the virus by drying the spinal cords and then ground up this material to make his vaccine. He not only developed a normal vaccine to protect persons or animals against becoming infected with rabies, but also developed the Pasteur prophylaxis, which could be administered to persons who had already been infected with rabies. When a person was infected with rabies, the first symptoms did not develop until 3 weeks or more later. Immunity could be established in less time with a series of injections of the Pasteur prophylaxis. In 1885, Pasteur administered his prophylaxis to Joseph Meister, a 9-year-old boy who had been bitten in fourteen places by a rabid dog. The boy did not develop rabies. Soon afterwards, Pasteur administered the treatment to a 14-year-old shepherd boy named Berger Gupile, who had become a hero by struggling with a rabid dog to prevent it from biting some younger children. Again the prophylaxis saved the boy from developing the fatal disease. As word of these successes reached the public, Pasteur became an international celebrity. This victory of germ theory over a particularly feared disease gave a tremendous boost to public acceptance of germ theory.

If Pasteur is the father of germ theory, then Robert Koch must be its godfather. Koch was a German biologist whose many contributions include the discovery of the germs of tuberculosis (TB) and cholera, and the development of the tuberculin skin test for TB. His most important contribution, however, was a set of four logical steps, known as "Koch's Postulates," to establish a causal relationship between a microorganism and a disease. In an 1882 paper in which Koch first announced his discovery of the tubercle bacillus, he states the postulates in a crude

form as a refutation to the argument made by some miasma theorists—that the germs he had found were symptoms of tuberculosis rather than the cause of it. Eight years later he stated them in their fully developed form, as follows:

> If one can now, however, prove: first, that the parasite in each individual case of the disease in question can be found and indeed under conditions which correspond to the pathologic changes and the clinical course of the disease; second, that it does not occur in any other disease as a chance and nonpathogenic parasite; and third, that it is capable of being isolated . . . from the body and in pure cultures sufficiently often transformed in order to cause the disease anew; then it can no longer be a random accident of the disease, but between the parasite and the disease can be conceived no relation except that the parasite is the cause of the disease. (Koch, 1890, p. 35).

The adoption of such strict and clearly logical standards for establishing causation greatly strengthened the case for germ theory. The postulates are entirely consistent with germ theory's contention that every disease is caused by a germ and by that germ alone. The possibility that infection with a germ might not cause disease in every instance was as alien to the germ theorists' assumptions as was noninfectious disease.

Koch, however, was to run into problems with the application of his own postulates to his isolation of the cholera bacillus. He had no difficulty in meeting the requirements of the first three postulates: present in all cases and at all stages, not present in other diseases, and isolated from the body in pure cultures. But he could not satisfy, the fourth postulate (often referred to as "experimental disease") by causing the disease anew with that culture. In the first place, he encountered this difficulty because the cholera bacillus is what is known as an obligate parasite—one that can live as a parasite only in a single species of animal—in man. It was impossible, therefore, for Koch to produce the disease in any laboratory animal. It was soon demonstrated, however, that the problem went beyond the inability to produce the disease in other animals. The German hygienist Max von Petenkoffer, and the French biologist and nutritionist Elie Metchnikoff, both opponents of germ theory, repeatedly drank glasses of cultures isolated from fatal cases of cholera without suffering any ill effects. In fact, no one has ever succeeded in producing anything more than mild diarrhea in volunteers given even massive amounts of the cholera bacillus.

Koch developed tuberculin in his search for a vaccine against tuberculosis. Although tuberculin proved to be ineffective as a vaccine, it produced an allergic reaction in persons who were infected with the tubercle bacillus. This provided the basis for wide use of the TB skin test in screening for tuberculosis. When Koch injected himself with tuberculin he experienced a very severe allergic reaction, indicating that he himself had a massive TB infection even though he never suffered the disease. This was one more situation incompatible with germ theory's simplistic equation of infection with disease.

In the following chapter we will discuss how classic epidemiologic theory arose, first as a refinement of germ theory, and eventually as its replacement.

Recommended Reading

Dubos, R. (1959). *Mirage of health.* Garden City, NY: Doubleday and Company. [Especially useful are Chapters 4 and 5.]

Haggard, H. W. (1929). *Devils, drugs and doctors.* New York: Harper and Brothers. [Especially Chapters 4 (regarding Semmelweis), 16 (Pasteur), and 17 (Hippocrates and Galen).]

Rosen, G. (1958). *A history of public health.* New York: MD Publications.

Winslow, C. E. A. (1923). *The evolution and significance of the modern public health campaign.* New Haven: Yale University Press. Reprinted in 1984 by the *Journal of Public Health Policy Inc.*, South Burlington, VT.

CHAPTER 2

Classic Epidemiologic Theory

As the inadequacies of germ theory became increasingly evident, epidemiologists began to rethink the causation of disease. This new and broader formulation was perhaps most clearly stated by Theobald Smith in his 1934 book, *Parasitism and Disease.* Concerning himself only with the infectious diseases, Smith explained disease as an instance of parasitism, in which the infectious agent lives in or on the human host. He saw disease as the result of forces within a dynamic system consisting of the agent of infection, the host, and the environment—which came to be known as the *epidemiologic triad.*

In terms of this model, patterns of disease depend on factors that determine the probability of contact between an infectious agent and a susceptible host. The route by which the agent is shed by an ill host, the length of time over which it is shed, the climatic conditions surrounding the host, and the presence of alternate nonhuman hosts that may serve as a continuing reservoir of infection all play a part in determining whether a host will be exposed to infection. The availability of susceptible hosts depends on population density and mobility, community vaccination status, and extent and degree of immunity from previous infections with the same or related agents.

Eventually, the concept of agent was generalized beyond infectious agents. Many epidemiologists found that this model was applicable to noninfectious diseases as well as those with infectious agents. The term *agent* had to be reconceptualized beyond infectious organisms. In terms of this broader conceptualization, the agent is the one factor that *must* be present for the disease to occur (as the smallpox virus, for example,