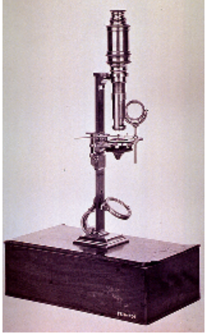

# 1 Introduction

What is the greatest contribution that medicine has made to humanity? In 2007, more than 11,000 readers of the *British Medical Journal* were surveyed to answer that question. The answers were (in order): (i) public health sanitation; (ii) discovery of antibiotics; (iii) discovery of anesthesia; (iv) discovery of vaccination; (v) discovery of the structure of DNA; and (vi) discovery of the germ theory of disease (1). Of the greatest contributions ever made to medicine, four of the top six were either the discovery of the germ theory of disease or innovations that were a direct result of that discovery. While the answers to this provocative question can be argued, the germ theory remains one of the most important contributions in the 2,500-year history of Western medicine and a relatively recent one—only 150 years old.

Modern society has taken for granted the value of public health sanitation; the vanishing of vaccine-preventable diseases such as smallpox, measles, and polio; and the existence of antibiotics to treat infectious diseases. In the 1970s, we even had the hubris to declare infectious diseases "conquered." However, infectious diseases have emerged or reemerged to devastate our modern world. I didn't realize when I made my decision to go into the specialty of infectious diseases in 1978, my last year of medical school, that I would be witness to this emergence. I thought that antibiotic treatments could actually cure people, not just treat them. Unlike chronic illnesses such as diabetes, bacterial pneumonia or a urinary tract infection, once treated with antibiotics, could be cured. I was not alone in this thinking.

I entered the specialty at a time when it was believed that medical science had nearly done it all—that there would be little left to do since we had such powerful

*Germ Theory: Medical Pioneers in Infectious Diseases*, Second Edition. Robert P. Gaynes.

agents for treating and curing infectious diseases. I recall my first meeting of the Infectious Diseases Society of America in 1981, when one of the foremost authorities in the field told the audience that "all infectious disease doctors would be doing in the next decade would be culturing each other." This complacency would be short-lived; such complacency has always been short-lived in medicine. During the same meeting, James Curran, at the time working at the Centers for Disease Control (CDC) and now recently retired as dean of the Rollins School of Public Health at Emory University, was scheduled to describe the first cases of what would soon be called AIDS (acquired immunodeficiency syndrome). Curran was the last of four speakers in a session that began with 150 people in the audience. But word of these cases had spread through the conference. By the time Curran spoke, over 1,000 people had crammed into a room at a downtown hotel in Chicago, IL. Even though the attendees at the meeting were told that infectious diseases were "conquered," the infectious disease community of doctors, microbiologists, and public health officials had clearly recognized that something new was happening.

Many new diseases, such as AIDS, hepatitis C virus, hantavirus, SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), Zika, and COVID-19 infection, have been described in the last 40 years. The microorganisms that cause these diseases were not actually new—they clearly existed before medical science became aware of them. In some cases, new techniques were developed to identify organisms that had always been there but that we could not detect. More often, the novelty for many of the new diseases is not the emergence of a new microorganism but the novel way the pathogen found its way into humans. Microorganisms are now thought to trigger diseases long considered to be chronic in nature, including peptic ulcers, numerous cancers, arthritis, type 1 diabetes, and others. In 1981, no one imagined how one of these newly emerged diseases, AIDS, which is caused by human immunodeficiency virus (HIV), would change the human landscape of entire continents, alter our conceptual framework of how we treat or even think about an infectious disease, and completely confound our understanding of the human immune system and vaccine development. Additionally, the upheaval caused by a virus causing respiratory disease that began in China at the end of 2019 was almost unimaginable until it spread rapidly through the world, resulting in the worldwide COVID-19 pandemic, a story that is still being scripted at the time of this writing.

Consider the vast changes wrought by HIV. In sub-Saharan Africa, HIV has completely altered the human demographics. For many decades, even centuries, before HIV, infectious diseases were the leading cause of death in Africa, but the deaths were childhood deaths. Malaria, infectious diarrhea, measles, and other childhood infectious diseases took their toll on the youngest inhabitants. As tragic as it sounds, most children in Africa did not see their first birthday, a fact that was simply accepted. The dynamic was high birth rates and high childhood death rates. In the course of a generation, HIV became the leading cause of death in Africa, but the deaths were not childhood deaths. The mortality rates among adults from HIV exceeded even the highest childhood mortality rates. In 2007, according to the Joint United Nations Program on HIV/AIDS, 60% of all HIV infections in the world were in Africa, even though Africa has only 12% of the world's population. In 2007, the life expectancy in Africa was 47 years with HIV and 62 years without HIV. In 2022, Africa remains the most severely affected region, with nearly 1 in every 25 adults (3.4%) living with HIV and accounting for more than two-thirds of people living with HIV worldwide (https://www.who.int/data/gho/data/themes/hiv-aids#cms). The medical, economic, social, and political effects of this one infectious disease are so great that the capacity to cope with its burden is stretched thin and, in many cases, has nearly collapsed. Curran was a witness to AIDS during its first 40 years in our modern world and described it this way:

> When you walked in the Castro district [of San Francisco] in the early 1990s, AIDS was palpable. The same thing is still true in some African cities. The hospital wards of African hospitals are filled with AIDS patients, sometimes two to three to a bed with young adult people dying. An AIDS death prior to antiretroviral therapy was a horrible process for most people. They lost weight, became demented, had unremitting diarrhea, Kaposi's lesions all over themselves, and people did not want to be near them. (J. Curran, unpublished data)

In Africa, while mortality for HIV-positive patients has improved since 2007 (see chapter 17, PEPFAR Successes), this kind of lonely, horrific death still occurred more than 420,000 times in 2021. HIV has forced a change in our social attitudes. Consider the sexual attitudes before HIV appeared. For centuries, syphilis was the most feared sexually transmitted disease since it could not be effectively treated until the 20th century. During the early 1900s, this disease became treatable with arsenic-based compounds. The concern about syphilis virtually disappeared with the introduction of penicillin. In the 1960s and 1970s, people had the perception that there were no incurable sexually transmitted pathogens. True, genital herpes existed and was a concern. While genital herpes was incurable, it did not cause death and could be treated with medicines. Sexual health could simply be managed by a visit to the doctor. Along came HIV. Once its sexual transmissibility was established, we were faced with a sexually transmitted pathogen that not only could not be handled by a trip to the doctor but also caused death. Sexual practices and attitudes changed. Among adolescents, for example, the rate of unprotected sex has decreased (2). But relentless efforts are needed for each new generation to implement these behavioral interventions.

The medical community itself has been forced to change its thinking because of HIV. Biologically, the silent nature of the infection, i.e., the long incubation period of years, even decades, leaves us with tens of millions of human incubators. Many HIV-positive individuals do not even know that they are infected. When the CDC reported the first five AIDS cases in 1981, an estimated 250,000 people were already infected with HIV in the United States alone. HIV has a silent, long incubation period followed by a lingering illness. Infectious disease physicians were just not equipped to face a chronically ill patient population in such vast numbers. The appearance of HIV/AIDS forced a complete reexamination of what we thought we knew about treating infectious diseases. Contrast HIV to influenza, which crashes into a community and leaves in a few short weeks. With HIV, an infectious disease becomes a chronic illness.

As the established paradigms for treating vast numbers of AIDS patients broke down for infectious disease doctors, public health officials struggled with the time-honored models they had used for monitoring infectious diseases. When a new infectious disease enters a community, it is often called an epidemic. The Merriam-Webster dictionary defines an epidemic as the occurrence of more cases of a disease than would be expected in a community or region during a given period of time. With some infectious diseases, an epidemic is easy to spot. Often, making the determination that more cases of an infectious disease have occurred than would be expected in a region can be challenging. One initial and basic approach used in public health to make this determination is development of an epidemic curve, a technique I learned on my first day of work at the CDC. After a known exposure, the number of cases of an infectious disease is plotted against the time of onset of illness among individuals with the disease to graph an epidemic curve. The shape of the epidemic curve might suggest the mode of transmission of the infectious agent. An epidemic curve where all the cases show signs of infection at nearly the same time and the number of cases quickly tapers off suggests that an infectious agent was transmitted from a common source, e.g., contaminated food at a picnic. With a different type of infectious disease, e.g., influenza, the curve may show an initial or index case, followed by two cases, then four, then eight, etc., until all individuals who are susceptible in a community have acquired the infection and the number of new cases decreases. This shape of an epidemic curve suggests person-to-person transmission of an agent. There are combinations of shapes in epidemic curves, but the overall shapes of these curves are the same. The number of cases goes up and then comes back down. In public health, the goals are to shorten the epidemic or work to prevent the problem or a similar problem from occurring, i.e., decrease the width and/or height of the epidemic curve and prevent the occurrence of any epidemic curves in other communities. This is the infectious disease epidemic paradigm. Doctors and public health officials were accustomed to this approach. In fact, we thought we were pretty good at it. HIV was different. HIV produced a chronic infectious disease, one in which the virus entered the body, remained silent (although it could be transmitted) for years, and then produced a lingering disease in which the virus did not disappear in an individual while he or she remained alive, even during treatment. The curve measuring HIV cases went up but did not come back down. Other viruses, such as hepatitis B or C virus, had long incubation periods before illness developed and were known before HIV. However, only a portion of patients initially infected with hepatitis B or C developed chronic illness, although we continue to grapple with people with chronic liver disease from hepatitis B and C. The rapid spread of HIV was coupled with an almost completely ineffective immune response from a person who had the virus. The virus was not eliminated by antibody production. In fact, HIV went on to damage the very immune system we had always thought would eliminate a pathogen. HIV's ravage of the immune system left the person susceptible to other infectious agents that he or she would normally not be susceptible to, so-called opportunistic infections. In the first few years of AIDS, it was invariably fatal within 4 years of an AIDS diagnosis. No one was prepared to deal with an infectious agent that could produce disease like this. The mentality of the medical community had to change to deal with a chronic infectious disease. Public health turned to the chronic disease experts for guidance on how to predict, moderate, and control it. We could not cure HIV and move on to something else. In the United States, we have been somewhat comforted by the success of treatment of HIV, which has improved dramatically since the mid-1990s. Life expectancy of adults with HIV infection who take combination antiretroviral drug therapy may now be near that of life expectancy of individuals without HIV infection (3). Still, treatment does not cure the individual. Indeed, intermittent treatment often leads to changes, i.e., mutations, in HIV that result in treatments that are ineffective or more difficult to administer, a problem that has troubled infectious disease management since the advent of modern antimicrobial therapy. Success in HIV treatment in the United States and elsewhere remains challenging and expensive. In Africa and other less developed regions, the prospect of treatment has improved since 2010 but there are still more than 27 million people in Africa with HIV. The cost of drugs and the infrastructure to deliver and monitor drug treatment will remain substantial. The "what goes up must come down" or epidemic thinking will not solve HIV or other endemic infectious diseases, such as tuberculosis or malaria, in Africa. We have had to reconsider our infectious disease treatment/prevention model to one that effectively approaches chronic or endemic infectious diseases. According to Curran, "this model is far less heroic, but arguably more important. And that's why there needs to be a change in thinking" (Curran, unpublished).

Nowhere has HIV challenged our conceptual framework more than in the development of an HIV vaccine. The world desperately needs an effective immunization for HIV as the means to control or even eliminate AIDS. Immunizations have been one of the most effective methods for control of disease, even eradicating the scourge of smallpox. The traditional approach to immunization formulation is to kill or inactivate a pathogen and inject it into people. Vaccines formulated in this way rely upon duplicating a successful human immune response to the natural exposure of a pathogen. Following the discovery of HIV as a causative agent of AIDS in 1983, the expectation was to rapidly develop a vaccine but, as of 2022, we still do not have a licensed vaccine. Progress has been hindered by the extensive genetic variability of HIV. We still do not have a complete understanding of immune responses required to protect against HIV acquisition (4). The traditional methodology of vaccine development has not worked for HIV.

HIV has been the most visible pathogen that has changed the concept that infectious diseases could be conquered, a concept that, according to Curran, "is now not credible" (Curran, unpublished). We have every reason to believe that other microorganisms might find their way into humans as we carelessly expand our way into previously undisturbed ecosystems. A new pathogen emerging anywhere in the world is cause for worldwide concern. The most obvious example is SARS coronavirus-2 (SARS-CoV-2). The rapid geographic dispersal of this virus causing COVID-19 infection is a clear reminder of how small our world has become. But there are other worries that shake our notion that infectious diseases have been subjugated.

The complacency that led us to the notion that we have conquered infectious diseases was due to our apparent successes—immunizations and antibiotics. Until HIV, development of vaccines was a major success of our modern medical world. The chief difficulty was administering the vaccines to the people who needed them. Vaccines were and still are underutilized. But immunizations can only prevent illness. Antibiotics treat illness. From the discovery of the first antibiotic, medical science and microorganisms have been in a constant struggle. Since the beginning of modern antibiotic therapy, resistance to antibiotics has steadily increased, and it is increasing faster than we can discover new therapies. Recent discoveries of vancomycin-resistant *Staphylococcus aureus* and bacteria containing enzymes called carbapenemases that degrade some of the most potent antibiotics, the carbapenems, are but two examples of the difficulties facing contemporary treatment of infectious diseases. But we cannot simply blame the appearance of antibiotic-resistant pathogens on clever, evolutionary tricks of microorganisms.

The widespread resistance among bacteria is a problem largely of our own making. Antibiotic use leads to antibiotic resistance. While it is blatantly obvious, most health care providers generally ignore this statement. Our infectious disease treatment paradigm involves use of broad-spectrum antibiotics, usually without specific knowledge of the offending pathogens. There is hidden harm that occurs as a result of this antibiotic exposure. Sometimes a pathogen causing an infection will begin susceptible to the agent but become resistant to it during therapy. But often, antibiotic resistance is actually the result of collateral damage. The resistance develops among pathogens that are not responsible for the infectious syndrome manifested by the patient. Humans normally harbor bacteria in the mouth, the colon, the skin, and other sites. The normal bacterial flora in humans is immense and often protects the body when harmful bacteria invade. When powerful antibiotics destroy much of the normal, protective bacteria, the void is filled by small numbers of resistant bacteria that we all may harbor. These resistant subpopulations of bacteria are given a chance to proliferate after antibiotic therapy. The resistant organisms may not even cause damage to the person treated with broad-spectrum drugs, but this person may become a reservoir or a human factory of a silent source of resistant organisms to those around him. Infection control efforts often fail since no one may be aware that the recently treated individual harbors antibiotic-resistant organisms. The number of people colonized but not infected with a resistant organism may be 50 times greater than the number of people who have an infection with a resistant organism. This so-called iceberg effect, where most of the resistance problem is hidden below the surface where we cannot see it, has been best described for hospitals, but resistance has become a problem outside hospitals. Community-acquired methicillin-resistant *S. aureus* (MRSA) infecting large numbers of patients who had not been in hospitals has been described in recent years. MRSA can be spread from one person to another. Our attempts to limit spread of this organism through infection control efforts appear to have been largely ineffective. Current attempts at hospital-based efforts to control MRSA are controversial and may be too little, too late, since so many MRSA infections now occur outside hospitals. Indeed, determining the effectiveness of control measures for MRSA or other resistant microorganisms is complex. Ultimately, the reservoir of the resistance will be found to involve exposure to antibiotics, perhaps in a person's distant past or in another person who served as the source of the MRSA.

The proliferation of antibiotic-resistant organisms is challenging the current tenet of infectious disease practice—use broad-spectrum antibiotics to "kill the bugs" with little or no concern for the collateral damage of antibiotic resistance. We have abused one of our greatest medical treasures, antibiotics. Abuse of antibiotics has opened the door to a new era with untreatable antibiotic-resistant infections, a post-antibiotic era. Pharmaceutical companies are not going to bail us out of this problem, since most have limited or even eliminated antibiotic drug discovery programs, largely because of economics. For example, from 2019–2022 there were no new antibacterial antibiotics approved by the Food and Drug Administration in the United States (https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2022). While some progress has been made in the last 25 years, finding new antibiotics has been time-consuming, difficult, and expensive, with no guarantee of success.

The dilemmas from newly emerging infectious diseases—HIV, an often fatal, chronic infectious disease, and SARS-CoV-2, which have stressed, to the breaking point in some places, our ability to prevent infection, find treatment, and provide it to millions; HIV vaccine failures that require a complete reassessment of the concepts of the human immune response; untreatable, antibiotic-resistant infections that portend a post-antibiotic era; and the unsettling notions that new pathogens like SARS-CoV-2 or a microorganism that causes disease even worse than COVID-19 infection will likely emerge, and that a problem that emerges in one corner of the globe can be rapidly transported anywhere in the world—have forced the medical and public health community to scrutinize itself. Medical science must reconsider all approaches to detecting and diagnosing emerging infectious diseases, to developing vaccines, to discovering new antibiotics, and to using wisely the precious few antibiotics that we have.

Where do we start? Before we can figure out where we should go, we should examine how we got here. We should look back to our initial advances in understanding infectious diseases. Appreciating how major contributions were made by some of the greatest doctors in history will help us reconsider our approaches to the practice of infectious diseases. Just as economists and policymakers look back to the Depression to develop policies to relieve us from economic woes, we should examine the history of infectious diseases. Historians debate the best approach to study the past. Thomas Carlyle, a well-known historian in the mid-1800s, once wrote, "The history of the world is but the biography of great men" (5). As an amateur historian, I have chosen to view history this way in order to detail the lives of 13 men and 2 women who were pioneers of our current conceptual framework of infectious diseases. Here, I must make a few qualifying remarks. First, the conceptual framework for the practice of infectious diseases is from Western medicine. This book is largely limited to Western medicine. Some readers may have a limited appreciation for the Eurocentric approach. Yet while my purpose is not to glorify Eurocentric concepts, Europe is where our conceptual framework for the practice of infectious diseases medicine was conceived. Contributions from other cultures, as germane as they are to a holistic perspective on the method of discovery, were largely ignored by Western medicine—often to its detriment. Second, there will be those who question the choice of the individuals who were included. While I doubt that one can argue against those included in this book, the persons excluded from any discussion will no doubt generate controversy. I have chosen individuals whose contributions were essential to understanding the origins of our approach to the practice of infectious diseases medicine and whose stories were compelling to me. I will admit to small detours into anecdote to better understand the person. The influences on the lives of these discoverers, often early influences, the era in which they lived, their personalities, and, in many cases, their daring, permitted these individuals to make extraordinary contributions even when those contributions were not initially well received. Discoveries made by an individual need to be accepted into the practices of the community before they can actually become advances. As we shall see, at times, the discovery had little impact until the practices of the community were reevaluated. These reexaminations provide lessons and, perhaps, some hope as we are forced to look introspectively toward our own practice of infectious diseases medicine.

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