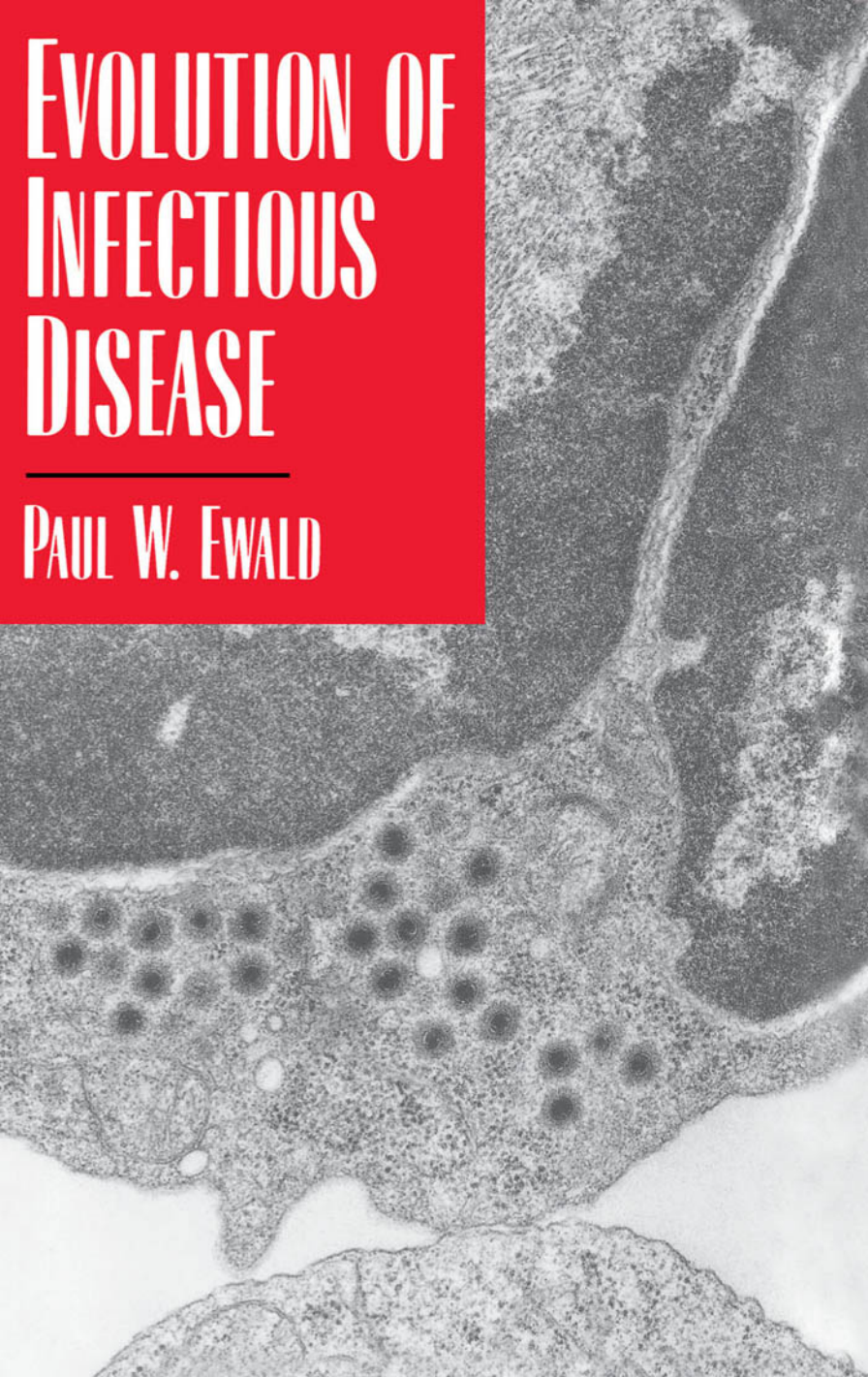
Evolution of Infectious Disease

Paul W. Ewald



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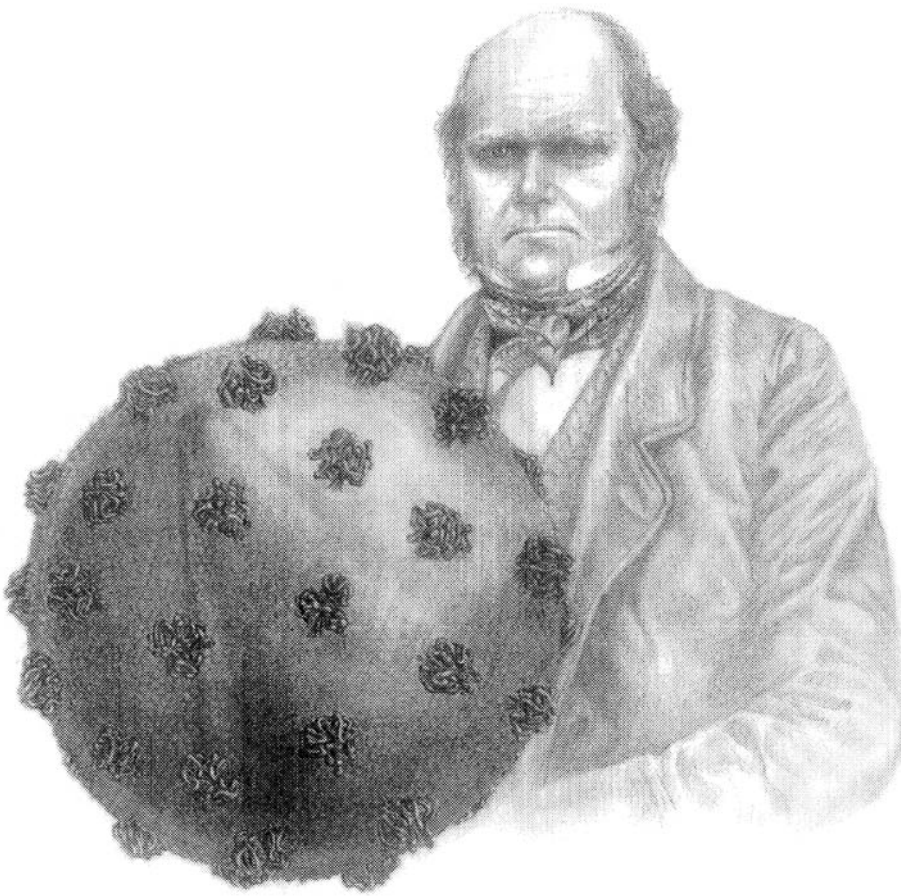

Evolution of Infectious Disease

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The frontispiece represents the merging of evolutionary biology, symbolized by Charles Darwin, with current knowledge about infectious processes, symbolized by the human immunodeficiency virus. The conical capsule inside the virus encloses the virus's genetic instructions. As discussed in Chapter 9, the projections from the virus's surface (called gp120) allow the virus to enter white blood cells by attaching to receptors (called CD4) on the surface of the cells, much like a hand grasps a doorknob to enter a house. *Illustration by Jennifer Nolan.*

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Acknowledgments

When I was a graduate student, I, like most graduate students, spent time wondering what insights I might eventually have and where they would come from. And, like most students of ecology and evolution, my mind would wander to the classic, romantic stories in this field: Charles Darwin generating the principles of natural selection from his observations of finches in the Galapagos, or G. Evelyn Hutchinson gaining insights about the structure of ecological communities by peering into a pool full of aquatic insects in front of the little church of Santa Rosalia on the outskirts of Palermo, Sicily. Hutchinson entitled the paper that grew from his insights "Homage to Santa Rosalia." If I were to follow Hutchinson's lead, I would have to call this book "Homage to Manhattan, Kansas" because my impetus to apply evolutionary insights to the health sciences originated from a rather bad case of diarrhea that I acquired while I was conducting research near a little garbage dump on the outskirts of Manhattan, Kansas. Between the urgent dashes, I had long stretches of time to ponder the broader significance of my predicament. A chain of questions began forming. Should I treat the diarrhea or should I let it run its course? Why was this particular organism causing me more problems than the other organisms that I had encountered during my previous 23 years? And why was it that even though I was in extreme discomfort, it was no worse? Unlike other agents of diarrhea, this bug was not a threat to my life.

The ideas presented in this book have taken shape over the ensuing 16 years to answer this chain of questions and the additional questions that each answer generated. I am particularly grateful to those scientists who, early on,

recognized the value of pursuing such questions and fostered my interest in doing so. Sievert A. Rohwer and Gordon H. Orians encouraged my early efforts to apply evolutionary principles to infectious disease and enlightened me about the relevance of evolutionary thinking whenever living things are the subjects of study. William D. Hamilton urged me to pursue these studies from our first meeting in 1978; he has also suggested that every evolutionary biologist should send me 50 dollars because the unification of evolutionary biology with the health sciences should help raise evolutionary biology's impoverished status in the minds of many outside the field. (If anyone is interested, that would be 70 dollars after adjusting for inflation.)

Many scientists contributed valuable ideas and perspectives during the middle and later stages of this work. Mary Jane West Eberhard helped me to recognize the value of comparative methods for fostering the integration of evolutionary biology and epidemiology, in part through her insights on Darwin's development of the principles of evolution. By never letting me off the hook during spirited exchanges, William G. Eberhard helped me to identify assumptions, weaknesses in arguments, and alternative hypotheses. David I. Ratner was always ready to provide mini-lectures on things molecular. My drawing together of information, ideas and arguments also benefitted from discussions with Richard D. Alexander, Roy M. Anderson, Tom Butynski, Geoffrey Cowley, Richard A. Goldsby, William B. Greenough, III, Jan Kalina, Jonathan Kingdon, Olga F. Linares, Elizabeth E. Lyons, Stephen S. Morse, Gerald Myers, Randolph Nesse, Gerald Schad, Robert Smutz, Andrew Spielman, James Strain, and George C. Williams. I thank Robert J. Biggar, Fernando Gracia, Moslem Udin Khan, Miguel Kourany, Leonardo J. Mata, Gerald Myers, Benjamin Schwartz, and H. Shimanuki for taking the time to clarify research findings and provide unpublished results. I note with appreciation the hundreds of scientists who have sent reprints and preprints of their work. William B. Greenough, III, Ethan J. Temeles, and George C. Williams provided numerous helpful comments on the manuscript, as did Nadine Alexander and Jennifer Nolan, who also expedited the final stages of manuscript preparation.

Many students have made contributions during discussions and by passing along relevant references. In particular, I thank Meg Abbot, Steve Bennett, Shagufta Bidiwala, Steve Boorstein, Beth Ellingwood, Tony Goldberg, Kathy Hanley, Marta Heilbrun, Kathleen McKibben, Karen Kiang, Lara Litchfield, Jennifer Nolan, Sarah Rubenstein, Jennifer Schubert, Bruno Walther, Kurt Weber, and Lowell Weiss. For help in obtaining articles and books I am grateful to Leeta Bailey, Margaret Groesbeck, Michael Kasper, Floyd S. Merritt, Susan Lisk, and Susan Edelberg of the Robert Frost Library at Amherst College, E. Tooke and P. Heddle of University of London's Book Depository, and the librarians at the London School of Hygiene and Tropical Medicine.

Many of the hypotheses presented in this book were developed and preliminary data were obtained while I was supported by the Michigan Society

of Fellows and the Division of Biological Sciences at the University of Michigan from 1980 to 1983 and by an NSF/NATO postdoctoral fellowship at Imperial College during 1984 and 1985. Amherst College nurtured the research since 1983 by granting a Miner D. Crary Fellowship, a Trustees Faculty Fellowship, an Amherst College Faculty Research Award, sabbatical funding, and logistical support. The work was also aided by a fellowship from the Occupational Health Program at Harvard School of Public Health. The later stages of research and the final drawing together of ideas into this book were made possible by a George E. Burch Fellowship in Theoretic Medicine and Affiliated Sciences awarded by the Smithsonian Institution and hosted by the Smithsonian Tropical Research Institute.

My parents, Sara and Arno Ewald, fostered during early formative years a tendency to look from different perspectives and explore interests wherever they may lead. Christine Bayer Ewald has been both a source of support and a source of sources throughout my work on the evolution of disease.

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CHAPTER 1

Why This Book?

Given enough time a state of peaceful coexistence eventually becomes established between any host and parasite.

Rene Dubos (1965)

Disease usually represents the inconclusive negotiations for symbiosis...a biological misinterpretation of borders.

Lewis Thomas (1972)

The ideal of parasitism is actually commensalism.

Paul D. Hoeprich (1989)

A BREAK WITH TRADITION

Few ideas have been so ingrained in the literature of medicine and parasitology as the idea that parasites should evolve toward benign coexistence with their hosts. Few ideas in science have been so widely accepted with so little evidence. And few ideas are so at odds with the fundamental principles on which they are supposedly based, with such a great potential for missed opportunity.

The proponents of this idea rarely trace it to fundamental evolutionary principles; when they do they reveal a misunderstanding of the most basic evolutionary process: natural selection. One can pardon the early proponents. Theobald Smith (1934), Hans Zinsser (1935), and N. H. Swellengrebel (1940) were writing at a time when evolutionary biologists were just beginning to integrate natural selection with their newly found understanding of genetics (Fisher 1930, Haldane 1932). Even those writing on the subject through midcentury can be excused. Until William D. Hamilton (1964) and George C. Williams (1966) clarified the process of natural selection, even prominent biologists focusing on evolutionary processes were more than a bit confused (e.g., Wynne-Edwards 1962, Lorenz 1964). As the time since Hamilton and Williams's landmark writings has passed from years to decades, however, the perpetuation of this idea that parasites inexorably evolve to benignness has become distressing; it serves as an indicator of just how disconnected modern evolutionary biology is from modern health sciences. In recent years both theoretical and empirical studies have led to a rejection of obligate evolution to benignness (Levin & Pimentel 1981, Anderson & May 1982, Ewald 1983, 1988, 1991a, Levin 1983, May & Anderson 1983), yet it is still presented in well-respected journals and medical texts as the foundation upon which evolutionary arguments are built (e.g., Palmieri 1982, Doyle & Lee 1986, Hoeprich 1989, Snewin et al 1991, Waters et al 1991).

The confusion of prominent biologists and medical scientists alike can be traced to a misunderstanding about the levels at which natural selection acts. When advocates of obligate evolution to benignness write on the subject, they often phrase their arguments in terms of what is best for the parasite species or for most individuals within the species (Holmes & Bethel 1972, Palmieri 1982, Hoeprich 1989). Burnet and White (1972), for example, state, "For Nature, survival of the species is all that counts." Simon (1960) writes that "attenuated infection represents a state in which the most favorable conditions are provided for the greatest number of individuals over the longest period of time." But there is no reason to presume that natural selection favors what is best for the greatest number of individuals over the greatest amount of time. Natural selection favors characteristics that increase the passing on of the genes that code for the characteristics. If more rapid replication of a virus inside of a person leads to a greater passing on of the genes that code for that rapid replication, then replication rate will increase even if the more rapid growth of the virus population within a person causes the person to be severely ill, or leads to an overall decrease in the numbers of the virus among people, or hastens the eventual extinction of the virus.

Proponents of obligate evolution toward commensalism write about how inefficient parasites are if they reproduce so extensively that they leave behind millions of progeny in an ill or dead host, and how this inefficiency is a mark of poor adaptation of the parasite to its host (Swellengrebel 1940, Thomas 1972).

But the number of lost organisms is not the relevant number. We might as well say that maple trees are poorly adapted because 990 out of every 1000 helicopter-like seeds are doomed to an early death. The number relevant to natural selection is the number of genes passed into the succeeding generation. Would the genes coding for production of 1000 seeds be left in greater numbers than the genes coding for production of 100 seeds? The 1000-seed strategy may be vastly more wasteful in terms of seed death and tissue destruction, but if it ultimately yields more trees in succeeding generations, it will be more efficient in terms of evolutionary success. So too, a parasite that reproduces massively inside a host, leaving billions of pathogens to die after the final transmission event, will contribute more genes for that rapid reproduction into future generations than a parasite that by virtue of its lower rate of reproduction leaves fewer organisms stranded in the host but gets its descendants into fewer hosts.

Indeed, looking at the problem from this perspective, one might wonder whether the less harmful, slower reproducers could ever win. How could they pass on more copies of their instructions for slower reproduction in the midst of competition with the fast reproducers? The resolution to this problem lies in understanding the potential for pathogens inside of a host to be very similar genetically. The population of viruses inside of a person may number in the billions, a number generated by growth of the virus population from a few successful colonists. As a consequence of this growth, a particular genetic instruction in one virus stands a good chance of being in many if not most or even all of the other viruses inside the person. If a gene regulates the virus's replication at a low level and restricts the degree of tissue invasion, it may lose out in competition with any faster-reproducing competitors inside the person. But if the illness caused by the fast replicators severely curbs the prospects for transmission, then people who by chance become infected with slowly replicating colonists might transmit their pathogens to other people and thereby to future generations at a faster rate than those infected with the rapidly replicating colonists.

This argument is tricky because the advantages that the slower replicators achieve through slower reproduction are shared with any rapidly replicating cohabitants. The slow reproducers therefore tend to lose when they cohabit a person with fast reproducers. But because the population of pathogens in a person tends to grow from a few colonists, they may be genetically similar to one another; a slow replicator will often cohabit a person with other slow replicators, and fast replicators will often cohabit with fast replicators. The slow replicators will contribute more to succeeding generations when slow replication sufficiently enhances the chances for transmission to new hosts. [Those versed in the terminology of evolutionary biology will recognize that this process represents cooperation or altruism among the pathogens, which is generated by the inclusive fitness effects (Hamilton 1963, 1964) of slow replication; one can say that the slow replication evolves by kin selection (Maynard Smith 1964)]. When slow

replication does not enhance transmission sufficiently, the more harmful fast replicators will be favored. Similarly, if the specifics of mutation, transmission, or pathogen reproduction increase the genetic variation of the parasites within a host, the slow replicators may be disadvantaged (Wilson 1980). Although many variations on the theme exist, these tradeoffs are fundamental to the application of natural selection to the evolution of host–parasite relationships. More generally, understanding these tradeoffs provides the key to understanding the evolutionary paths that our disease organisms have taken in the past and will take in the future. By studying these tradeoffs this book attempts to identify the circumstances that favor evolution toward any particular level of harmfulness, from extreme benignness to lethality.

Prior to the last quarter of the twentieth century, a scattered few scientists have disagreed with the conventional wisdom that adaptation should lead inexorably to benign states of coexistence. The malariologist G. R. Coatney and his colleagues (1971) expressed their reservations, writing that the "body of evidence is, in our view, somewhat less than convincing." The virologist C. H. Andrewes (1960) also distanced himself from the traditional view, although haltingly. While affirming his belief in the idea that efficient parasites are benign, he observed that when pathogens are transferred into new hosts, they may increase in virulence, and concluded that pathogens evolve toward an intermediate, "optimum" virulence to facilitate transmission. He illustrated this idea with the sneezes and coughs of respiratory diseases, which may facilitate transmission by distributing pathogens in the environment.

The strongest disagreement with the traditional viewpoint came from Ball (1943), who focused on a corollary of obligate evolution toward benignness: that particularly severe disease is an indication of a recent and imperfectly evolved association. He attacked this idea by showing the numerous exceptions, and concluded that if there is a tendency for parasites to evolve toward benignness, it is of no predictive value because knowledge about virulence does not provide knowledge about the duration of the association between host and parasite. Ball's criticisms, like the more guarded warnings of Andrewes (1960) and Coatney et al. (1971), were ignored largely, I think, because none of these authors provided a general alternative framework for understanding why different host–parasite associations have evolved different levels of virulence. Without the advancement of such a framework, the idea that host–parasite relationships should evolve to a state of benign balance was apparently too appealing to be rejected, in spite of the fact that there was no good evidence for it. Since the late 1970s this situation has changed. We can now see not only an alternative framework but also the beginning of two new disciplines that are emerging from the controversy: disciplines that synthesize our knowledge about treatment of disease, spread of disease, and evolution, from the submicroscopic realm of molecular biology to the superorganismal realms of ecology and evolutionary biology.

EVOLUTIONARY EPIDEMIOLOGY AND DARWINIAN MEDICINE

Evolutionary biology is so firmly integrated with the rest of biology that it is not possible to mark a boundary between them. But modern medicine has been a peninsula. It is broadly and firmly connected with most regions of biology such as anatomy, physiology, biochemistry, molecular biology, and genetics, but has just a few thin bridges traversing the gulf to evolutionary biology. Knowledge about the evolution of antibiotic resistance is perhaps the best developed bridge between the disciplines. The discovery of the evolutionary basis for sickle cell anemia—protection against malaria—is another.

There are probably many reasons for the paucity of bridges. One stems from inadequate appreciation of the pervasiveness of evolutionary principles. From secondary school through medical school, the fundamental relevance of evolution to all of human life often has been ignored or even suppressed. Had it been different, the ideas presented in this book probably would have been addressed decades sooner, perhaps as early as a half-century ago, when evolutionary biologists were uniting the principles of genetics and natural selection. As will become clear in the pages that follow, the redress of these oversights may be a life-or-death matter for millions of people each year, and a quality-of-life matter for tens of millions more.

Realizing that scientists writing about the evolution of virulence have been incorrect throughout most of the last century is one thing; finding out what is correct is quite another. Application of evolutionary principles does not lead to the conclusion that all parasites evolve toward benignness. But can evolutionary principles help us understand why some parasites cause severe disease while others are nearly always extremely mild? This book is a dogged attempt to resolve this question and to understand the implications of this resolution for the future of the health sciences, in theory and in practice.

The question is at the heart of an emerging discipline: evolutionary epidemiology (Ewald 1988). Traditional epidemiology investigates the prevalence and spread of diseases within and among populations of hosts over ecological time scales. Epidemiology broadened the previous emphasis of health practitioners, which was on care of sick individuals, to a larger scale: the nature of disease processes among populations of individuals. Evolutionary epidemiology broadens the scale of inquiry still further to assess how the characteristics that traditional epidemiology has identified to be important—lethality, illness, transmission rates, prevalences of infection—change over time as hosts and parasites evolve in response to each other and to outside environments.

The integration of evolutionary biology with the health sciences is also spawning an overlapping discipline, termed Darwinian medicine, which takes an

evolutionary approach to the entire spectrum of issues related to health and disease (Williams & Nesse 1991). Darwinian medicine and evolutionary epidemiology are complementary in several ways. Whereas evolutionary epidemiology focuses on the spread of diseases, Darwinian medicine focuses more on the individual patient. Darwinian medicine, for example, encompasses treatment of psychiatric disorders and physical trauma, and emphasizes the evolutionary molding of developmental processes and genetic diseases. Central to both disciplines is the action of natural selection, but because Darwinian medicine focuses more on individual patients, it gives more attention to human evolution. From the perspective of Darwinian medicine, senescence, for example, is an inevitable consequence of selection for traits that are beneficial during the early and middle years of a maximum life-span. These traits eventually take a toll during old age, but by the time this toll comes due in nature, the organism may have already died from other causes. Natural selection, therefore, favors the senescent developmental arrangement: Buy now, pay later. The immediate fitness benefit outweighs the cost of deferred payment because organisms tend to die young in nature: A 30-year-old man killed by a mastodon will never pay the price of a heart attack brought on by decades of atherosclerosis.

Defining epidemiology broadly to include nonhuman hosts, evolutionary epidemiology spans a broader spectrum of host–parasite relationships; it extends beyond medical settings to encompass parasitism in nature and agriculture involving both plant and animal hosts. The two disciplines overlap broadly, especially where the interpretation and treatment of human infectious diseases are concerned. Both disciplines emphasize that appropriate patient care requires an understanding of the evolutionary processes affecting the disease-causing organisms and the responses of the host to these organisms.

Because the evolution of human characteristics is relatively slow, evolutionary epidemiology and especially Darwinian medicine consider time spans that encompass the evolution of *Homo sapiens* and even our ancestral species in which relevant characteristics, like immunological defenses, may have evolved. Pathogens, in contrast, may evolve substantially over time periods of a few weeks. When considering infectious diseases from the pathogens' "point of view," a few decades of medical records may offer a potential for evolutionary change that is comparable to the entire time span of our genus *Homo*. The evolutionary process for pathogens is therefore best considered to be a process in progress. The pathogens are a moving target of our research. We and our activities are part of the environment that pushes this process down one course or another. The following pages emphasize evolutionary epidemiology. George Williams and Randy Nesse offer a complementary overview of Darwinian medicine (Williams & Nesse 1991).

In preparing this book, I have tried to eject specialized terms whenever possible. Technical terms are superb for transmitting complex ideas rapidly and concisely to colleagues, but they create viscous barriers to interested outsiders.

And if there is one thing that a synthesis of evolution and the health sciences needs, it is input from outsiders. People in the health sciences need the foundation of evolutionary principles as much as they need the foundations of molecular biology. Evolutionary biologists need to grasp the complex and specialized knowledge of immunology, molecular biology, and medical treatment if they are to provide evolutionary insights into medical problems. Because evolutionary changes in disease organisms depend on past, present, and future cultural environments, historians, sociologists, anthropologists, and psychologists need to be involved. Perhaps most importantly, if we want people outside of the health sciences to continue to foot the bill for expensive long-term research, and to make intelligent decisions about which bills to foot, the information must be accessible to those outside of science and academia.

Having said all of this, I must concede that there are some terms, like evolutionary fitness, ribonucleic acid (RNA) and virulence, with which I could not part. To help readers with these stragglers, I have provided a glossary at the end of the text. Some terms that I use will mean different things to different people. When I use these terms I shall try to be clear about the definition that I am using. When I use the term *parasite*, for example, I am referring to any organism that lives in or on another organism and causes harm to that organism. Theoretically, I define *harm* as a negative effect on a host's evolutionary fitness. *Evolutionary fitness*, in turn, is a measure of the individual's success at passing on its genes into future generations through its survival and reproduction. In practice, however, we can rarely measure this effect; moreover, effects of disease that might drastically reduce the fitness of humans living in nature may have no negative effects on fitness in our modern society. In practice, then, we can think of harm, crudely, as the presence of illness and increased chances of death that result from parasitism, keeping in mind the important caveat discussed in the next chapter: Many aspects of illness may actually be beneficial rather than harmful to the host. When I use the term *virulence*, I am referring to the degree of harm to the host caused by the parasite. I use *parasite virulence* when I am writing about the degree to which the parasite's characteristics impose negative effects on the host. The flip side is *host resistance*. When resistance is lowered, a disease may be more virulent, even though the parasite's inherent virulence is unchanged. Together these two components, parasite virulence and host resistance, determine how negatively the host will be affected.

My emphasis will be from the parasites' point of view rather than from the hosts'. It is not that I have any fondness for the smallpox virus or the cholera bacterium, or even our ubiquitous companion, the common cold virus, whose virulence is high enough to trigger special attention from parents and spouses, but mild enough to allow its victim to savor this care. No, I emphasize the parasites' point of view because the health sciences have strongly emphasized the humans' point of view. This concern for humans has led health scientists to investigate in striking detail how host characteristics influence virulence; indeed, tremendous

progress has been made from this perspective. We are now learning how diet, exercise, stress, and genetic differences between people affect the severity of our illnesses. Every year, general principles are refined and applied to new situations. Throughout history, for example, there has been general awareness that physical fitness and a good diet make people better able to ward off disease. This general awareness has been gradually transformed into a finely woven understanding of countless threads of information. The threads may seem contradictory at first, but eventually we see that the apparent contradiction arises from the difference between our imagined pattern and the real pattern. Early on, health scientists discovered that our immune systems are more able to combat infection when we have an adequate intake of vitamins, protein, and other nutrients. More recently, the negative effects of overintake of these nutrients—particularly fats, sugars, salt, and cholesterol—have been clarified. When dietary fats are restricted, for example, heart disease is reduced and our immune systems operate more effectively. Still more recently, researchers have identified beneficial effects of what once would have been considered severely restricted amounts of food. When laboratory animals are fed just enough food to meet their needs, they have lower rates of cancer, longer life-spans, and improved immune responses. Dietary restriction may even improve abilities to fight off infectious diseases such as influenza (Effros et al. 1991), although it may have the opposite effect in some diarrheal diseases (Greenough & Bennett 1990).

Modern health sciences have been particularly perceptive and ingenious when discerning the how our bodies work in health and disease. Modern health sciences have not been particularly perceptive or ingenious when addressing the long-term reasons why our bodies and their pathogens act the way they do. This book will *not* recount the marvelous achievements in the former category, but, rather, will point out the inadequacies in the latter. My hope is that by recognizing these shortcomings and setting out to remedy them, we shall generate a more farsighted approach to infectious disease. The short-range approach of the past assesses what our medical policies can accomplish, given the current characteristics of our disease organisms. The long-range approach of the future adds an evolutionary dimension to this assessment. It asks how our medical, social, and political activities have changed and will change these relationships by changing the disease organisms themselves.

WHY STUDY THE EVOLUTION OF DISEASE?

Because the answer to this question will vary from person to person, I shall try to answer it only on a personal level. By spelling out the reasons why I think this problem is worthy of our attention, I hope that I may help the reader to customize his or her own answer to the question.

One reason I want to understand the evolution of parasitism stems from the pervasiveness of the parasitic mode of life: Most of the species on our planet are parasites (Price 1980). We cannot understand nature and our place in nature without understanding parasites. But I, like most humans, am anthropocentric. As much as I value other species, I value human life more. Although I have tried to divorce my values from my assessments of the evolutionary processes that occur between host and parasite, the subject matter itself cannot escape being a reflection of these values. As a consequence, I tend to focus on the parasites that cause humans the most suffering and death. If we understand why diseases cause this suffering and death, we have a better chance of alleviating these effects.

Besides these general reasons for learning about the evolution of disease, there are some practical personal reasons. Each of us will have many encounters with infectious diseases. When they occur we need to decide on a best course of action. Should we treat our symptoms or should we let them run their course? Determination of the appropriate treatment requires application of evolutionary thinking. Yet modern medicine has been largely inattentive to this application. Until this inattentiveness is remedied, the patient and doctor together must take up the slack. In the absence of hard data, this process will inevitably be sloppy, but a sloppy, educated guess is better than a random guess. A framework for making these guesses and for structuring future research is outlined in the next chapter.

At a larger scale, policymakers must be cognizant of evolution to determine how to fund medical research and interventions for improving health. This need has always been pressing for people in poorer countries who have never had a respite from widespread death due to infectious diseases. It was less pressing for people in richer countries during the middle decades of this century. In the fourth edition of *Natural History of Infectious Disease*, Burnet and White (1972) stated, "Young people today have had almost no experience of serious infectious disease. The classical pestilences, smallpox, plague, typhus and cholera have been banished effectively for a hundred years or more and in the last half century the standard childhood infections have progressively lost their power to kill." AIDS has changed this rosy outlook for the wealthy countries and has further burdened the labored progress of less wealthy countries toward this goal. A general theory for the evolution of disease should be able to explain more than the decline of the classical pestilences and standard childhood infections. It should also be able to explain why this new pestilence has arisen, how it may evolve in the future if we continue our present policies, and what we can do to change this future evolutionary course.

At various places in this book I hold up Burnet and White's book to what may seem like wrathful scrutiny. Actually, I admire their book for its attempt to integrate epidemiology with ecology and evolution, but I contrast my ideas with

theirs for several reasons. First, their book is one of the most lucid and thoughtful of the many books and articles written on the ecology and evolution of disease. Among medically oriented people, it has become the standard analysis of infectious disease from an ecological and evolutionary perspective. I think, however, that rigorous applications of ecological and evolutionary principles will often lead to rejection of their conclusions.

I also wish to make these contrasts because people in the health sciences often seem to evaluate my arguments like lightning and then tell me to read Burnet and White, who already wrote the book on the subject. By showing explicitly how application of current evolutionary thinking differs from "the book on the subject," I hope that I shall cause a pause in readers who might otherwise view this book as merely supplemental to previous books that interpret disease as a temporary state of imbalance in an otherwise balanced Nature.

When the apparent imbalances arise, they may be caused by old pathogens in new places or by altered pathogens. Old pathogens in new places present no problem for traditional arguments. Their high virulence can be explained by insufficient time for accommodation between host and parasite. The altered pathogen is what draws out the murkiness in traditional arguments.

An article from a news magazine of science offers an illustration (Weiss 1989a). Encapsulating views from leading thinkers in epidemiology and disease history, the article analyzes whether devastating epidemics might arise in the future. But nowhere in the expert testimonies is there any consideration of an evolutionary mechanism. The speculations on future epidemics are instead made by analogy with past epidemics. The article begins, for example, by describing a six-month influenza epidemic that resulted in the deaths of more than 17 million chickens in Pennsylvania, and then quotes a well-respected virologist as saying that the world's human population is like Pennsylvania's chicken population; that is, large numbers of humans are vulnerable to an explosive and lethal epidemic, just as the large numbers of chickens in Pennsylvania in 1983 were vulnerable. The implicit assumption of this argument is that large numbers of hosts are vulnerable to highly lethal epidemics as long as the right mutation comes along. New plagues are ascribed to mutation without considering whether the harmful or the benign variants within the population of mutants will be more successful. The traditional approach considers the first step in the evolutionary process (that heritable genetic variation is created), but not the second step—the sieve of natural selection. Researchers have thus concluded that severely lethal epidemics will occur in the future, but their focus on mutation leaves them with no foundation for predicting which kinds of parasites will be the progenitors of the lethal outbreaks, how bad the lethal outbreaks will be, or how we can reduce the lethality of the outbreaks that do occur by suppressing the evolution of increased virulence.

To be sure, the 1983 chicken epidemic had its human counterpart—a pandemic of influenza that began toward the end of 1918 and killed about 20 million people

before it subsided about a year later. But why did the highly virulent rather than the less virulent influenza variants spread through our species in 1918 (and the Pennsylvanian chickens for that matter)? Conversely, why have all of the other influenza epidemics since then been so much less lethal? I think that we can begin to provide reasonable answers to these kinds of questions by integrating the fundamental principles of evolutionary biology with our knowledge of epidemiology. Most of what I have to say in this book is an attempt to do just that.

More generally, I am trying to use this book to reach people in the health sciences who are interested in looking beyond the currently prescribed boundaries of their fields. But I am also writing to reach biologists with an interest in the health sciences, and anyone else who shares an enthusiasm for learning why we are the way we are. I want people to see that evolution is not just something we should learn about to make us more broadly educated. It is that, but it is also going on around us all the time and is having deeply relevant effects—effects that could determine whether we and our loved ones will live or die. And no organisms are evolving faster with more pressing consequences than are the parasites among us: from the parasites of our agricultural resources, to the vectors of our lethal diseases, to the protozoa, bacteria and viruses that will kill millions of us this year. If we want to understand and manage our world better, we had better try to understand the evolution of infectious disease.

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CHAPTER 2

Symptomatic Treatment (Or How to Bind *The Origin of Species* to *The Physician's Desk Reference*)

EVOLUTIONARY FUNCTIONS OF SYMPTOMS

"You're just treating the symptoms." This admonition derives from the idea that problems are the effects of underlying causes, and to resolve a problem fully one must nullify the underlying cause. Applying the idea to infectious diseases, a twentieth-century physician might say that treating the symptoms of a disease may provide some comfort to the patient, but it is generally of little consequence to the future course of the problem at hand.

A physician with a firm grasp of evolutionary principles would disagree. The consequence of treating a symptom depends on the reasons why the symptom has evolved. One who argues "You're just treating the symptoms" is tacitly assuming that symptoms are side effects of an infection. An evolutionarily astute observer recognizes that symptoms might be just side effects, but they might represent adaptations that benefit the host or the parasite. For easy reference, I shall call the former a *defense* by the host and the latter a *manipulation* of the host (Ewald

1980), and I shall use *symptom* broadly to encompass both objective signs of disease and subjective manifestations.

Host defenses can be behavioral, morphological, physiological, or biochemical; they can provide repair to host tissues, barriers to invasion, protection from toxins, destruction of parasites, or inhibition of parasite multiplication. Manipulations by parasites alter the host's behavior or physiology to help convert host tissues into parasite growth and reproduction or to facilitate transmission to new hosts. The route through which manipulations benefit the parasite may be circuitous, if, for example, the alteration involves counterdefenses that permit evasion or neutralization of host defenses. [Williams and Nesse (1991) provide a similar breakdown, and Hart (1990) provides a framework for understanding the spectrum of behavioral defenses.]

The decision to treat or not to treat a symptom should depend on whether the symptom is a defense, manipulation, or side effect. If a symptom is a defense against the invading organism, symptomatic treatment may decrease the ability of the host to overcome the disease. On the other hand, if a symptom is a manipulation of the host by the parasite, symptomatic treatment may help the host recover or help control the spread of the disease to other hosts.

DEFENSIVE SYMPTOMS AND FEVER

Virtually all symptoms of infectious diseases can be explained hypothetically as a defense, but fever is the most frequently cited example. What to do about fever has been a source of controversy throughout history. In Greek writing, it was seen as part of the disease, the state of imbalance among the "humours." In more recent centuries, expert advice about fever depended more on the expert consulted than on the current state of evidence. Over the past two decades the controversy has continued, but the focus of the controversy has shifted to experimental evidence instead of "expert" opinion. For this shift we can thank Matthew Kluger, who had the insight to choose as his study subject the desert iguana (*Dipsosaurus dorsalis*). Prior to Kluger's insight, people were focusing on animals that generated their body heat internally. To reduce fever, an experimenter would have to do some fairly major messing about with an animal's physiology. Consider, for example, use of aspirin. When fever is reduced with aspirin, so are pain, the inflammatory response, and other processes that could help the animal defend itself against parasites. If such aspirin treatment worsened disease, one would not know whether this exacerbation resulted from reduced fever or the sabotaging of other activities that were helping to control the infection. Realizing that desert iguanas keep their body temperatures constant and warm by shuttling between warm and cool microhabitats, Kluger suspected that they might run fevers by moving to even warmer microhabitats when they are infected. When he infected the iguanas with a bacterium called *Aeromonas*

hydrophila, he found that they did run a fever. He then conducted the critical experiment, which showed that infections became more severe when iguanas were kept at the lower temperatures preferred by uninfected iguanas (Kluger et al. 1975).

But just because a symptom is a defense against one kind of parasite does not mean that it is an effective defense against a different species or even a genetically different parasite of the same species. In fact, there are good theoretical reasons for presuming that fever will not always function as a defense. Most obviously, some pathogens will be more resistant than others to febrile temperatures. Because the turning off of a febrile response to these pathogens would require prolonged host evolution in response to the particular pathogen, there very well might be insufficient time for such a response. But even if there is sufficient time, hosts may have limited options. Shutting down the febrile response to one kind of pathogen might also turn off the response to other pathogens that trigger fever by the same mechanism. This restriction of host options could allow pathogens to manipulate the system in their own favor.

Consider a pathogen that is not suppressed by fever. Because metabolic processes generally speed up with temperature, such a pathogen could conceivably benefit from the high temperatures, producing more progeny in a given period of time. The host would have limited options for dealing with this threat. Turning off the fever response to this pathogen could cause the host to suffer more harm from other pathogens which would no longer be suppressed. Given enough time, we might expect the host to evolve a mechanism for distinguishing between fever-resistant and fever-susceptible pathogens, but time is on the side of the pathogens, which have a greater potential for rapid evolution. Growth of laboratory strains of the polio virus, for example, is typically inhibited by febrile temperatures, but if the virus is grown in the lab at febrile temperatures, it rapidly evolves an improved ability to withstand them (Lwoff 1959).

Evolutionary logic provides clues about where to look for pathogens that benefit from fever. The proportion of infections that trigger fever varies greatly among the different pathogen species. Like pathogens grown in the lab under high temperatures, pathogens that virtually always trigger fevers would be under strong selective pressure to develop abilities to reproduce under febrile conditions. If there are pathogens that benefit from fever, those uniformly associated with fever would therefore be prime candidates.

Another part of the spectrum may encompass pathogens that are neither suppressed nor enhanced by fever. If the host can differentially respond to such pathogens, then one would not expect them to trigger fever because such fevers would harm the host.

A survey of the existing information on fever does reveal a great variety of outcomes. One of the agents of lizard malaria, *Plasmodium mexicanum*, grows just as well at febrile temperatures as it does at normal temperatures; accordingly,

it does not trigger fever in one of its primary hosts, the western fence lizard (Schall 1990). Whether this lizard generates a fever in response to any parasite, however, is unknown.

Grasshoppers and their parasites not only illustrate this point but also show how resolution of these ambiguities may have important consequences for agriculture. During their population explosions, grasshoppers may parasitize bumper crops, transforming them into stubble in a matter of days. Yet, the grasshoppers, too, may be ravaged by parasites. Especially lethal are *Nosema* protozoa and *Entomophaga* fungi–two groups of sit-and-wait parasites (see Chapter 4) that reproduce massively inside of grasshoppers, often killing them within a week or two.

One of these pest species of grasshoppers, *Melanoplus sanquinipes*, runs a behavioral fever when infected with *Nosema acridophagus* (Boorstein & Ewald 1887). Grasshoppers kept at these febrile temperatures survived longer and gained weight more rapidly than when they were kept at the temperatures preferred by uninfected hoppers (Boorstein & Ewald 1887); however, a closely related parasite, *Nosema locustae*, did not trigger a fever in the same species of grasshopper (Hanley 1989).

Such variations in febrile responses have consequences for the usefulness of parasites for biological control programs. If *Nosema* are used in biological control programs, their effectiveness would depend on which species is used and the temperature ranges available to the hoppers in nature. On hot sunny days, the *M. sanquinipes* would be able to combat infections with *N. acridophagus* by running high fevers, and little if any control of the hopper populations by the parasite would be expected. During cool cloudy days, control would be feasible. Historical data are consistent with this idea: In northern latitudes, outbreaks of *Melanoplus* and other grasshopper species tend to occur during hot, sunny years (Edwards 1960, Gage & Mukerji 1977).

Even when a symptomatic defense *is* triggered by each of two closely related parasites, the parasites may be different in their susceptibility to the defense. Grasshoppers infected with a U.S. strain of the fungus *Entomophaga grylli* sunned themselves, generating a fever of 100°F, which destroyed the fungus. But an Australian variety of this fungus was resistant to such a fever (Anonymous 1989a, Carruthers et al. 1992).

Fever in mammals is associated with a variety of immunological changes that could either enhance or inhibit effective control of pathogens (Lorin 1987). Because of these associations and the internal heat production of mammals, the evidence for and against a defensive role for mammalian fever seems to be especially difficult to interpret. When rabbits and mice are kept in warm environments, they have higher body temperatures and are better able to survive life-threatening infections (Lwoff 1959). But these experiments do not separate any negative effects of high temperature on the virus from correlates of the higher body temperature. Mammals kept in cold environments may die more often

because their higher metabolic rates at cold temperatures drain resources that could otherwise be used to produce virus-fighting armaments such as antibodies.

Suppression of *moderate* fevers of rabbits with aspirin seemed to harm their chances of surviving infections with the bacterium, *Pasteurella multocida*, whereas suppression of *intense* fever did not have this effect (Kluger & Vaughn 1978). But because these fevers were suppressed with aspirin one cannot distinguish the effects of fever from the effects of the other aspirin-induced changes in the rabbits. A reciprocal experiment provides some additional support for a defensive role: rabbits treated with a fever-suppressing drug can control *Hemophilus influenzae* and *Streptococcus pneumoniae* better when they are artificially heated (O'Reilly & Zak 1992). Local application of an anti-febrile drug directly on the brain's temperature control center, similarly increased the mortality of rabbits (Kluger 1991). On balance, the data support the view that fever often defends mammals against pathogens (Kluger 1991), but it may not always do so (Banet 1986, Blatteis 1986).

When fever does tend to inhibit bacteria, it seems to do so at least in part by reducing the availability of iron levels in the body and simultaneously raising the bacteria's need for iron (Grieger & Kluger 1978, Kluger & Rothenberg 1979). But iron limitation may not inhibit viruses, and many bacteria may actually cause more severe illness when deprived of iron. A paucity of iron, for example, stimulates the production of toxins by *Escherichia coli* (a cause of diarrhea), *Vibrio cholerae* (the agent of cholera), *Corynebacterium diphtheriae* (the agent of diphtheria), and a destructive hospital-acquired pathogen called *Pseudomonas aeruginosa* (Miller et al. 1989, Schmitt & Holmes 1991). If fever reduces the availability of iron, it may cause more toxin to be produced, possibly worsening the infection. In this case, fever could be a weapon that backfires, causing worse disease than would be present without fever.

Evolutionary and biochemical principles therefore suggest that the overall net effect of fever may be positive or negative, depending on the particular association between pathogen and host. Because these alternative evolutionary scenarios have not been generally recognized, key experiments to distinguish between them have not been done. As a consequence, we have made only the first few steps toward understanding the degree to which fever represents a defense or a manipulation or neither across the multitude of pathogens that activate fevers.

TREATMENT OF DEFENSES

So, should you take cold medicine or not? Television commercials barrage us with products that stop "all 12 cold symptoms"—twelve chances to sabotage a defense and 12 chances to nullify a manipulation! But even the less comprehensive cold medications can leave a person in a quandary. Symptomatic

treatment of the common cold with aspirin increases the total duration of infectiousness (Stanley et al. 1975, Graham et al. 1990). In one study, treatment increased the density of released viruses but did not alter perceptibly the intensity of illness; in another study, treatment did not increase the rate at which viruses were released, but worsened the nasal congestion. Sabotage of the febrile defense is probably not a viable explanation for these results because the rhinovirus that caused these colds triggers little if any fever, and the nasal temperature of even febrile hosts does not rise above the optimal temperature for viral replication (Stanley et al. 1976). In another study, aspirin administered well after the onset of infection did not alter the duration of infectiousness (Mogabgab & Pollock 1976); any defense sabotaged by aspirin apparently tends to protect people during the first day or so of infection.

But what defense has been sabotaged? Aspirin reduces inflammation, fever, and pain. Acetaminophen (sold under the brand name Tylenol) reduces fever and pain. If the reduction in inflammation is the sole reason for the prolonged infections with rhinovirus, then perhaps treatment of colds with acetaminophen would be acceptable. But like aspirin, acetaminophen prolonged the period of viral multiplication even though it does not reduce inflammation (Graham et al. 1990). As mentioned above, a sabotaging of fever is also an unlikely explanation. That leaves pain. By reducing the pain associated with illness, symptomatic treatment may make a person more active (Doran et al. 1989) and, as a result, might compromise the ability of the immune system to keep the viruses in check. If the reduction in pain is responsible, then other painkillers, like ibuprofen, should also cause a worsening of the infections. Patients treated with ibuprofen did have worsened symptoms and increased viral shedding, but these differences were not statistically significant, possibly because of the small number of patients in each group. Worsening of rhinovirus infections through the sabotaging of defensive pain is therefore still a viable explanation. Alternatively, aspirin might interfere directly with the immune system. Whatever the actual mechanism, symptomatic treatment of colds seems to have relatively minor consequences because the common cold virus is so inherently benign.

A greater risk from symptomatic treatment occurs when disease organisms are inherently more dangerous. Chickenpox, for example, is slightly more dangerous than the common cold, and influenza is more dangerous than chickenpox. Treatment of chickenpox with acetaminophen prolonged the period of itchiness and time until drying of scabs, which marks the end of viral shedding (Doran et al. 1989).

When outbreaks of influenza and chickenpox occur, virtually all infected people recover, even without treatment (99.95% & 99.997%, respectively). But as a scattered few are well on their way to recovery, they may begin vomiting repeatedly. A few hours later they become confused and delirious. Within a few days about one-fourth will be dead. This classic picture of Reye's syndrome illustrates the dangers of symptomatic treatment. Reye's syndrome tends to occur