EVOLUTION OF VIRULENCE

EVOLUTIONARY CONSIDERATIONS of host–parasite interactions provide a fascinating topic for experimental and theoretical biologists. I use the term "parasite" to denote anything that lives and multiplies inside another organism and usually causes some harm. Phages are parasites of bacteria. Many viruses and bacteria are parasites of humans. There are many single and multicellular eukaryotic parasites that cause infectious diseases in humans and other animals. Our genome contains "parasitic" DNA that simply wants to increase its own abundance without much concern for other genes.

Parasites are as old as life itself. As soon as there were self-replicating machines, there were parasites to exploit them. Much of the design of individual cells and higher organisms can be explained as an adaptation to defend against parasites and limit the damage that is associated with infection. Bacteria have enzymes to cut viral genomes into pieces. Plants produce a vast library of chemicals in self-defense. The vertebrate immune system is a highly complicated, costly organ with the task of protecting against infectious agents. Even sexual reproduction has been explained as an adaptation to maintain genetic

diversity and to help evolve away from parasites. In return, sexually transmitted parasites use this mode of reproduction of their hosts to their own advantage.

The conventional wisdom of many medical textbooks has been that well-adapted parasites are harmless to their hosts. This notion is based on the argument that killing its host does not help a parasite that relies on its host for reproduction. Some well-known observations seem to support this view. A much-cited example is the evolution toward reduced virulence of the myxoma virus in Australian rabbit populations. A more recent example, which we encountered in the previous chapter, is the observation that long-standing primate lentivirus associations seem to be apathogenic. Simian immunodeficiency viruses (SIV) apparently do not cause disease in their natural hosts. These viruses and their hosts have been coevolving for millions of years. In contrast, the human immunodeficiency virus (HIV) entered the human population only a few decades ago and causes a fatal disease.

There are also many counterexamples, however, where long-standing host–parasite systems have not evolved to become harmless. A major example is human malaria, which is estimated to have caused more human death than any other infectious disease. Another well-known example is provided by nematodes in fig wasps. These nematodes have a strong detrimental effect on their host, despite the observation that fig wasps preserved in twenty-million-year-old amber have already been infected by nematodes.

Mathematical epidemiology is one of the oldest disciplines of theoretical biology. In 1760 Daniel Bernoulli, hoping to influence public health policy, developed a mathematical model to evaluate the effectiveness of variolation against smallpox. In 1840 William Farr performed a statistical analysis of deaths from smallpox in England and Wales. In 1908 Ronald Ross, who had discovered that malaria was transmitted by mosquitoes, formulated a simple mathematical model to explore the relationship between the prevalence of mosquitoes and the incidence of malaria. William Ogilvy Kermack and Anderson Gray McKendrick, in 1927, established the important "threshold theory": introducing a few infected individuals into a population will cause an epidemic only if the density of susceptibles is above a certain threshold. In 1979 Roy Anderson and Robert May formulated many new approaches for theoretical epidemiology and laid the foundation for much subsequent work.

They developed simple mathematical models in order to explain laboratory experiments or epidemiological data. They also studied ecological questions by analyzing how infectious agents regulate the population size of their hosts. They emphasized the importance of the "basic reproductive ratio" and its consequences for vaccination programs.

May and Anderson also point out that parasite evolution does not necessarily lead to avirulence, but instead selection works to increase the parasite's basic reproductive ratio, R_0. If the rate of transmission is linked to virulence, then selection can favor increasing virulence. They reanalyzed the classical myxoma virus infection of Australian rabbits and argued that evolution had led to intermediate levels of virulence. The data actually suggest an equilibrium distribution of viruses with different levels of virulence; after many years, both the most virulent and the least virulent virus strains are still present in the virus population. Most infections are caused by virus strains with intermediate levels of virulence.

In this chapter we will study the evolutionary dynamics of parasites, but will assume that the host does not evolve on the time scale that is under consideration. This is a good assumption because, in general, parasites evolve much faster than their hosts. We begin by investigating the basic model of epidemiology, where parasite evolution maximizes the basic reproductive ratio. This result is based on the assumption that an already infected host cannot be superinfected by another parasite strain. We will subsequently remove this constraint and explore the evolutionary dynamics of superinfection. Superinfection means that an already infected host can be infected and taken over by another parasite strain.

In the classification of Anderson and May, this whole chapter deals with "microparasites," which typically include viruses, bacteria, and protozoans. They have small sizes, short generation times (compared with those of their hosts), and high rates of direct reproduction within their hosts. In contrast "macroparasites," which comprise parasitic helminths and arthropods, have longer generation times than microparasites and reproduce only very slowly within a host individual. Mathematical models for microparasites are typically formulated in terms of infected and uninfected (and immune/recovered) hosts. Models for macroparasites, in contrast, must keep track of the number of parasites in individual hosts.

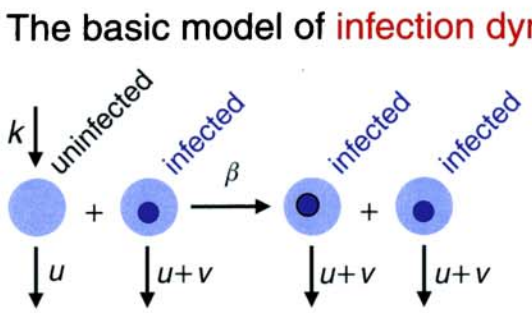

Figure 11.1 The basic model of infection dynamics describes the spread of an infectious agent (a parasite) in a population of hosts. An infected host meets an uninfected host and passes on the infection. It is often useful to think of biological dynamics as chemical kinetics: here an infected host "reacts" with an uninfected host to produce two new infected hosts. The rate constant of this reaction, β, denotes the infectivity of the parasite. The normal mortality of hosts is described by the death rate u. The disease-induced mortality (virulence) is given by v. Uninfected hosts enter the population at a constant rate, k.

11.1 THE BASIC MODEL OF INFECTION BIOLOGY

The basic epidemiological dynamics of a host–parasite interaction (Figure 11.1) can be described by the following system of ordinary differential equations

$$\begin{aligned} \dot{x} &= k - ux - \beta xy \\ \dot{y} &= y(\beta x - u - v) \end{aligned} \tag{11.1}$$

Uninfected and infected hosts are denoted by x and y, respectively. In the absence of the parasite, the host population is regulated by a simple immigration-death process, with k specifying the constant immigration rate of uninfected hosts and u their natural death rate. This represents a simple, if somewhat artificial, way of attaining a stable host population in the absence of infection. Infected hosts transmit the parasite to uninfected hosts at the rate βxy, where β is the rate constant characterizing the parasite's infectivity. Infected hosts die at the increased rate $u + v$. The parameter v defines the virulence of the infection; it is the excess mortality associated with infection. More generally, virulence can be defined as the parasite's effect on reducing the fitness of infected hosts.

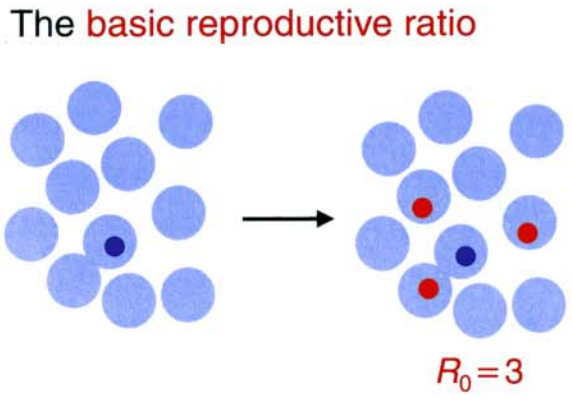

Figure 11.2 The basic reproductive ratio, R_0, of an infectious agent is given by the number of secondary infections that are caused by one infection that is introduced into an uninfected population of hosts. R_0 is a crucial quantity that determines whether or not a parasite can spread in a host population. If $R_0 < 1$, then the parasite will die out after a few rounds of infection. If $R_0 > 1$, then an explosive increase in the number of infections (an epidemic) will occur.

The basic reproductive rate of the parasite is defined as the number of new infections caused by a single infected host if introduced in a population of uninfected hosts (Figure 11.2). For system (11.1), the basic reproductive ratio is given by

$$R_0 = \frac{\beta}{u+v}\frac{k}{u}. \tag{11.2}$$

This can be understood as follows. The average lifetime of an infected host is $1/(u+v)$. The rate at which one infected host produces new infections is βx. The product of these two quantities is the average number of new infections caused by a single infected host in its lifetime if there are x uninfected hosts. The equilibrium abundance of uninfected hosts prior to the arrival of the infection is given by $x = k/u$. Hence equation (11.2) represents the basic reproductive ratio, R_0, which is a crucial concept of epidemiology.

If R_0 is less than one, then the parasite cannot spread. The "chain reaction" is sub-critical: a single case might cause a few additional cases, but then the transmission chain will die out again. An epidemic cannot take place.

If R_0 is greater than one, then the chain reaction is super-critical. There will be an exponential increase in the number of infected hosts. An epidemic will occur. After some time, the number of infected individuals will peak and then start to decline. Damped oscillations lead to a stable equilibrium given by

$$x^* = \frac{u+v}{\beta} \qquad y^* = \frac{\beta k - u(u+v)}{\beta(u+v)} \tag{11.3}$$

A successful vaccination program must reduce the population size of susceptible hosts such that the basic reproductive ratio is below one. If $R_0 = 5$, then more than 80% of the population must be vaccinated to prevent an epidemic. If $R_0 = 50$, then more than 98% of the population must be vaccinated. In general, successful vaccines are those that are directed against infectious agents with low reproductive ratios.

I call system (11.1) the "basic model of infection biology," because it describes not only the dynamics of an infectious agent in a population of hosts but also the dynamics of a virus within a single infected host. In the latter case, x and y denote, respectively, uninfected and infected cells. The application of this model to HIV infection is described in my book *Virus Dynamics*, coauthored with Robert May.

11.2 SELECTION MAXIMIZES THE BASIC REPRODUCTIVE RATIO

To understand parasite evolution, we have to study the epidemiological dynamics of at least two parasite strains competing for the same host. Extending equation (11.1), we obtain

$$\begin{aligned} \dot{x} &= k - ux - x(\beta_1 y_1 + \beta_2 y_2) \\ \dot{y}_1 &= y_1(\beta_1 x - u - v_1) \\ \dot{y}_2 &= y_2(\beta_2 x - u - v_2) \end{aligned} \tag{11.4}$$

The two parasite strains differ in their infectivity, β_1 and β_2, and in their degree of virulence, v_1 and v_2. The basic reproductive ratios of strains 1 and 2 are, respectively, given by

$$R_1 = \frac{\beta_1}{u + v_1} \frac{k}{u} \tag{11.5}$$

and

$$R_2 = \frac{\beta_2}{u + v_2} \frac{k}{u}. \tag{11.6}$$

Coexistence between the two parasite strains is only possible if $R_1 = R_2$, which is ungeneric. At equilibrium, the time derivatives, $\dot{x}$, $\dot{y}_1$, and $\dot{y}_2$, must be zero.

Furthermore, stable coexistence between strain 1 and strain 2 requires that both y_1 and y_2 are positive at equilibrium. From $\dot{y}_1 = 0$ and $y_1 > 0$, we obtain $x = (u + v_1)/\beta_1$. But from $\dot{y}_2 = 0$ and $y_2 > 0$, we obtain $x = (u + v_2)/\beta_2$. Both conditions can only hold simultaneously if $R_1 = R_2$. Generically, however, we expect that $R_1 \neq R_2$, in which case coexistence is not possible.

If both basic reproductive ratios are less than one, $R_1 < 1$ and $R_2 < 1$, then the only stable equilibrium is the uninfected population,

$$E_0: \qquad x = \frac{k}{u} \qquad y_1 = 0 \qquad y_2 = 0 \tag{11.7}$$

If $R_1 > 1 > R_2$, then strain 2 becomes extinct and the only stable equilibrium is

$$E_1: \qquad x^* = \frac{u + v_1}{\beta_1} \qquad y_1^* = \frac{\beta_1 - u(u + v_1)}{\beta_1(u + v_1)} \qquad y_2^* = 0 \tag{11.8}$$

If $R_1 < 1 < R_2$, then strain 1 becomes extinct and the only stable equilibrium is

$$E_2: \qquad x^* = \frac{u + v_2}{\beta_2} \qquad y_1^* = 0 \qquad y_2^* = \frac{\beta_2 - u(u + v_2)}{\beta_2(u + v_2)} \tag{11.9}$$

If both basic reproductive ratios exceed one, $R_1 > 1$ and $R_2 > 1$, then the strain with the higher basic reproductive ratio will outcompete the strain with the lower basic reproductive ratio. If $R_2 > R_1$, then all infected individuals will eventually carry strain 2, while strain 1 becomes extinct. The system will converge to equilibrium E_2.

Note that $R_2 > R_1$ is precisely the condition that strain 2 can invade equilibrium E_1. This means that the derivative $\partial \dot{y}_2/\partial y_2$, evaluated at equilibrium E_1, is positive. $R_2 > R_1$ is also the condition that strain 1 cannot invade equilibrium E_2. This means that the derivative $\partial \dot{y}_1/\partial y_1$, evaluated at equilibrium E_2, is negative. These derivatives characterize the growth rate of an infinitesimal amount of the invading strain at a particular equilibrium point. We conclude that E_1 is unstable, while E_2 is stable. Coexistence between the two strains is not possible. Therefore strain 2 outcompetes strain 1.

Therefore evolution will tend to maximize the basic reproductive ratio (Figure 11.3). If there is no constraint between infectivity and virulence, then the

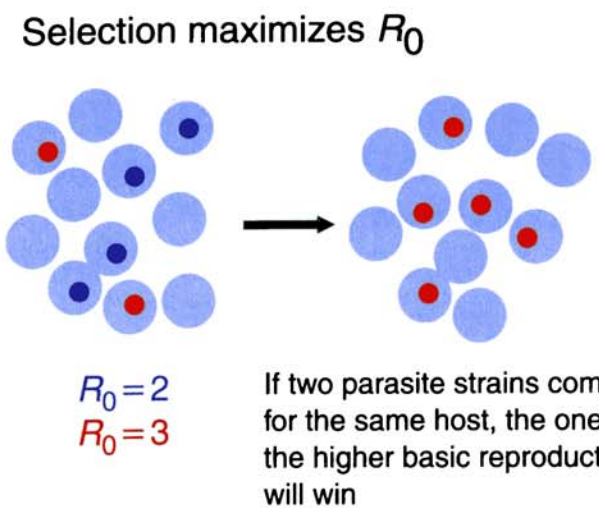

Figure 11.3 In simple models of infection dynamics, selection acts to maximize the parasite's basic reproductive ratio. If two parasites compete for the same host, then the parasite with higher R_0 will outcompete the other parasite. Therefore well-adapted parasites have a high R_0, but not necessarily low virulence.

evolutionary dynamics will increase β and reduce v. This represents the conventional wisdom that infectious diseases will evolve to become less virulent.

In general, however, we expect an association between virulence v and infectivity β; usually the harm done to hosts (v) is associated with the production of transmission stages (β). For certain functional relations between v and β there is an evolutionarily stable degree of virulence, corresponding to the maximum value of R_0. Other situations allow evolution toward the extreme values of very high or low virulences. The detailed dynamics depend on the shape of β as a function of v. It is interesting to note that along some trajectories where virulence increases, parasite evolution can lead to lower and lower parasite population sizes (in terms of total number of infected hosts).

If the infectivity is proportional to virulence, $\beta = av$, where a is some constant, then the basic reproductive ratio, R_0, is an increasing function of virulence, v. In this case selection will always favor more virulent (and therefore more infectious) strains.

If the infectivity is a saturating function of virulence, $\beta = av/(c + v)$, then the basic reproductive ratio, R_0, is a one-humped function of virulence. The maximum R_0 is achieved at an intermediate optimum level of virulence given by $v_{\text{opt}} = \sqrt{cu}$. If the virulence of a parasite population is greater than v_{opt}, then selection will reduce virulence. If it is less than v_{opt}, then selection will increase virulence.