

Trends and Perspectives

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1. Focus attention on developing and growing topics in parasitology.
2. Identify new and old problems in need of research.
3. Explain how results from one area of biology might have some bearing on current studies in parasitology.
4. Present teachers and students with concise summaries of recent discoveries and new theories.

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Coevolution of hosts and parasites

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INTRODUCTION

The coevolution of parasites and their hosts has both general biological interest and practical implications in agricultural, veterinary and medical fields. Surprisingly, most medical, parasitological and ecological texts dismiss the subject with unsupported statements to the effect that 'successful' parasite species evolve to be harmless to their hosts. Recently, however, several people have explored theoretical aspects of the population genetics of host-parasite associations; these authors conclude that such associations may be responsible for much of the genetic diversity found within natural populations, from blood group polymorphisms (Haldane, 1949) to protein polymorphisms in general (Clarke, 1975, 1976) and to histocompatibility systems (Duncan, Wakeland & Klein, 1980). It has also been argued that pathogens may constitute the selective force responsible for the evolution and maintenance of sexual reproduction in animal and plant species (Jaenike, 1978; Hamilton, 1980, 1981, 1982; Bremermann, 1980).

The present paper aims to take a line that is somewhat more empirical than most of the previous theoretical work. Defining parasites broadly to include viruses, bacteria, protozoans and helminths, we observe that the virulence of a parasite (the rate at which it induces host mortality) is usually coupled with the transmission rate and with the time taken to recover by those hosts for whom the infection is not lethal. Specifically, in mice, men and other vertebrates (Fenner & Ratcliffe, 1965; Burnet & White, 1972) and in many invertebrates (Maramorosch & Shope, 1975; Anderson & May, 1981) low virulence is generally associated with effective immunological or non-specific responses which tend to suppress pathogen replication, with a concomitant reduction in transmissibility. Using data for the epidemiological parameters characterizing the various grades of myxoma virus infecting rabbits in Australia, we show how in this particular case virulence may be expected to evolve to an intermediate value; the analysis appears to accord with the observed facts. Other examples are discussed in a more qualitative way. *In general, we conclude that the complicated interplay between virulence and transmissibility of parasites leaves room for many coevolutionary paths to be followed, with many endpoints.*

As a preliminary, it seems useful to present a brief overview and attempt at a synthesis of the diverse, scattered and growing body of theoretical literature on the coevolution of hosts and their pathogens.

EXPLICITLY GENETIC MODELS

One class of models deals explicitly with the population genetics of the host species, with the genetic structure of the parasite population being handled in various ways. In these models, the fitness of the different host genotypes are explicitly or implicitly frequency dependent. Density-dependent fitness effects, on the other hand, do not usually enter; that is, the interplay between epidemiological processes and population densities are not usually accounted for.

There is a substantial literature, largely relating to plant breeding, in which one specifies the fitness of various host genotypes when exposed to various parasite genotypes, and then studies the ensuing dynamical behaviour of the host and parasite gene frequencies (Mode, 1958; Person, 1966; Yu, 1972; Leonard, 1977; Lewis, 1981*a, b*; for biologically orientated reviews, see Van der Plank, 1975 and Day, 1974). Thus, for example, under the usual 'gene-for-gene' assumption, a one locus/two allele system in a diploid host may interact with a diallelic locus in a haploid parasite; the fitness W_{Aa} of the Aa host genotype will be a weighted sum over the fitness $w_{Aa,i}$ for this host when attacked by parasites of the genotype i (weighted by the gene frequencies of the haploid parasite genotypes i), and so on. The equilibrium and stability properties of such systems can be studied, once explicit assumptions are made about the magnitudes of the fitness constants ($w_{Aa,i}$) and the like. Although straightforward in principle, such dynamical studies can become very messy by virtue of the proliferation of parameters. These systems are clearly capable of yielding stable polymorphisms or stably cyclic oscillations between resistant and susceptible hosts and virulent and avirulent parasites; they can yield chaotic fluctuations in gene frequency. As Lewis (1981*a*) has recently emphasized, however, such polymorphisms do not automatically ensue: 'The intuitive arguments are sufficient to guarantee the existence of a polymorphic equilibrium, but not to guarantee its stability. There are conditions under which such equilibria may be stable; however, it seems that there are bounds on how different the virulent and avirulent reactions can be if there is to be stability.'

This style of analysis has the merit that the genetics of both host and parasite are treated explicitly. Epidemiological factors, on the other hand, are not really considered: if two or more strains of parasite are present, it is usually assumed that all hosts are infected, with the fraction of hosts infected by each strain being in simple proportion to the relative abundance of that strain (which, for a haploid parasite, means in proportion to the parasite gene frequencies). At best, it may be assumed that a constant fraction, x , of the host population escapes infection; this can introduce significant additional complications (Lewis, 1981*a*; Yu, 1972). But x is treated as one more phenomenological constant rather than as a dynamic variable determined by the interaction between host and pathogen populations.

In most of the models just discussed, whether framed as difference or as differential equations, it is assumed that host and parasite generations tick over on much the same time scale. This is a reasonable approximation for some interesting plant-parasite systems. The parasites of many animals, however, cycle through many generations in a single generation of the host, and are thus rapidly evolving compared with their hosts. In this event, it makes sense to study the genetic structure of the host population, subsuming the genetical dynamics of the

parasites in frequency-dependent fitness functions for each genotype of host. One way to do this would be to take the kind of 'gene-for-gene' analysis outlined above, and reduce the dimensionality of the system of equations by assuming the parasite dynamics operate on a faster time scale than the host dynamics, so that parasite gene frequencies are always at the equilibrium appropriate to the (slower changing) host gene frequencies. In this way one would have equations for the host gene frequencies, in which all the fitness functions were frequency dependent. To our knowledge, no one has adopted this approach. A second approach (Hamilton, 1980; 1981; Clarke, 1976; see below) is simply to make some *ad hoc* assumption about the frequency-dependent fitness functions of the various host genotypes – still without any explicit epidemiological analysis – and explore the possible range of dynamical behaviour.

A third approach is to let conventional epidemiological assumptions, of one kind or another, dictate the form of the frequency-dependent fitnesses of the host genotypes (Gillespie, 1975; Kemper, 1982; Anderson & May, 1982*a*). Gillespie's (1975) pioneering study initially assumes a population of haploid hosts, and explores the conventional metaphor of one locus with two alleles: individuals of the *a* genotype are resistant to some particular disease, but pay a cost in having a lower fitness (by a factor $1-s$) than the susceptible individuals who do not become infected; individuals of the *A* genotype are susceptible to the disease, and those individuals who actually contract the disease have their fitness decreased to $1-t$, which is lower than the fitness of the resistant individuals (i.e. $t > s$). Gillespie assumes the disease spreads through each generation in an epidemic fashion, in a manner described by the standard equations of Kermack & McKendrick (1927) (see also Kendall, 1956 and Bailey, 1975):

$$dX/dt = -\beta XY, \quad (1a)$$

$$dY/dt = \beta XY - vY, \quad (1b)$$

$$dZ/dt = vY. \quad (1c)$$

Here X , Y , Z are the number of hosts in a given generation of the susceptible population that are as yet uninfected, infected and recovered (and thereby immune), respectively. The coefficient β measures the transmission rate (and may itself depend on the magnitude of the host population), and v is the recovery rate. From these equations, it can be shown that the fraction, I , of the susceptible hosts that are affected by the disease is given implicitly, for these haploid hosts, by the relation:

$$I = 1 - \exp(-IpN/N_T). \quad (2)$$

Here N_T is the threshold host density, $N_T = \beta/v$, below which the disease cannot be maintained, N is the total host population density, and p is the frequency of the allele *A* (so that pN is the population of susceptible hosts). It follows that the fitnesses of resistant and of susceptible hosts, W_R respectively, are

$$W_R = 1 - s, \quad (3a)$$

$$W_S = 1 - It. \quad (3b)$$

The fitness W_S is frequency dependent, in a way that depends on the epidemiological assumptions that are embodied in equation (2). Gillespie (1975) subsequently

indicates how the analysis and broad conclusions extend to a diploid population in which the heterozygotes Aa are equivalent either to the susceptible AA individuals (A dominant) or to the resistant aa individuals (a dominant).

Gillespie's work shows that a stable polymorphism, with both susceptible and resistant genotypes (both A and a alleles) present, will ensue for a particular range of values of the fitness values s and t , and of the magnitude of the host population in relation to the threshold population, N/N_T . If the fitness cost of resistance, s , is relatively small, then the population will evolve toward all being resistant; if the fitness cost of contracting the infection t , is sufficiently small relative to s ($t \rightarrow s$), or if N is close to (or below!) N_T , resistance will not be present.

Gillespie's analysis can readily be extended to encompass diseases that are stably endemic, rather than sweeping in epidemics through each generation. Kemper (1982) has given a thorough treatment of the case of endemic infective agents that do not confer immunity (roughly corresponding, for example, to gonorrhea (Yorke, Hethcote & Nold, 1978) or to many viral infections of insects (Anderson & May, 1981)). The dynamics of this system is described by equation (1), except that there is no immune class Z and recovery is directly back into the uninfected but susceptible class X . For a haploid host, as above, the equilibrium fraction, I , of the susceptible hosts that are infected is then

$$I = 1 - (N_T/pN). \quad (4)$$

The definitions of p , N and N_T , and the subsequent analysis, are as outlined above, except that equation (4) replaces equation (2) in determining the frequency-dependent fitness function W_S of equation (3b). Like Gillespie, Kemper concludes that the selective pressure of the parasite produces a 'stable polymorphic equilibrium as long as the fitness of the immunity-producing allele is neither too large nor too small in comparison to the fitness of a diseased individual'.

For an endemic infection that does induce immunity (for example, measles, rubella or pertussis), the calculation of I is slightly more complicated; the fraction of susceptibles in any given cohort decreases with age (see, for example, Anderson & May, 1982b). For estimating the fitness of susceptible genotypes, equation (3), the fraction of the susceptible population that has acquired infection, I , is given approximately by (Anderson & May, 1982a)

$$I = 1 - \exp[-(T_c/L)(pN - N_T)/N_T]. \quad (5)$$

Here T_c is the cohort generation time (May, 1976), L is the average life-expectancy and p , N and N_T are as before. Again, the conclusions broadly accord with those of Gillespie and Kemper (Anderson & May, 1982a).

Very generally, these analyses make it plain that, were selective pressures always to favour the evolution of 'harmless' or 'avirulent' parasites (so that $t \rightarrow 0$), we would not expect to find polymorphisms in host susceptibility (or resistance) associated with such infectious agents. This prediction does not accord with the available empirical evidence, since variability in host susceptibility to infection by a specific pathogen appears to be the rule rather than the exception.

As mentioned above, a different approach is to investigate the genetical dynamics of a host population in which various kinds of frequency dependence are assigned to the fitness of the different host genotypes. Clarke (1976) has argued

that, in general, a variety of plausible biological mechanisms could result in a rare genotype enjoying a selective advantage over commoner host genotypes in the presence of parasites or predators. Numerical exploration of models embodying these ideas showed that stable, or cyclic, or chaotic polymorphism could result, depending on the strength of the frequency-dependent advantage that accrued to rarer genotypes. Clarke (1975, 1976) has suggested that many protein polymorphisms may be maintained in this way. Subsequent authors have given formal explications of the way cycles and chaos arise in these nonlinear systems (for example, Oster, Ipaktchi & Rocklin, 1976; May, 1979), leading to complex and non-steady genetic systems. The essential ideas here go back to Pimentel's (1968) 'genetic feedback' and to Haldane (1949).

Jaenike (1978) has gone further, making the tentative suggestion that frequency-dependent aspects of the host-parasite association may help explain the evolution and maintenance of sex in host populations. In an important series of recent papers, Hamilton (1980, 1981, 1982; Hamilton & Zuk (1982)) has explored these kinds of models for the genetical dynamics of host populations. He shows that provided the frequency dependence associated with resistance and susceptibility to parasites is sufficiently intense, such models can generate complex cycles in host gene frequency, and that 'in certain states of cycling sexual species easily obtain higher long-term geometric mean fitness than any competing monotypic asexual species or mixture of such' (Hamilton, 1980). Hamilton urges the bold notion that the widely discussed selective disadvantages of sex (Williams, 1975; Maynard Smith, 1978) may typically be outweighed by the advantages sexual recombination confers under the sort of strong frequency-dependent selective forces that the genetic interplay between host and parasites may often induce. Several testable hypotheses follow from these ideas (Hamilton, 1982). In particular, gene frequencies at a polymorphic locus should exhibit systematic changes from generation to generation if the polymorphism is maintained by Hamilton's cycling. We observe that some support for this conjecture is provided by genetic studies of gene frequency changes in populations of wild mice (Berry, 1980). Combining seven surveys of blood parasites in North American passerines, Hamilton & Zuk (1982) showed that among these bird species there is significant correlation between the incidence of chronic blood infections and striking sexual display (specifically, male 'brightness', female 'brightness' and male song).

MODELS BASED ON EPIDEMIOLOGY AND POPULATION INTERACTIONS

Other models seek to give a relatively accurate account of the density dependence and epidemiology of the interaction between hosts and parasites, without retaining the explicit genetics. These models examine the dynamic interactions between a host population and populations of different strains of a parasite; the genetics is crudely implicit in, for instance, the varying rates of transmission and virulence of different strains of the parasite.

Levin & Pimentel (1981) have recently used this approach to examine the coexistence or otherwise of a host population with two different strains of a pathogen: one of the strains is more virulent than the other, inducing a mortality rate, α_1 , which is greater than that due to the less virulent strain α_2 ($\alpha_1 > \alpha_2$);

both strains have identical transmissibility (susceptible individuals, on contact with an infected individual, acquire the infection at a 'transmission rate' β in both cases), but the more virulent strains can 'take over' individuals already infected with the less virulent strain (at a *per capita* transmission rate $\sigma\beta$). Denoting the populations of hosts that are susceptible, infected with strain 1, and infected with strain 2 by X , Y_1 and Y_2 , respectively, Levin & Pimentel (1981) described the dynamics of this system by the set of differential equations

$$dX/dt = aN - \beta XY_1 - \beta XY_2 - bX, \quad (6)$$

$$dY_1/dt = \beta XY_1 + \sigma\beta Y_1 Y_2 - (\alpha_1 + b) Y_1, \quad (7)$$

$$dY_2/dt = \beta XY_2 - \sigma\beta Y_1 Y_2 - (\alpha_2 + b) Y_2. \quad (8)$$

Here a is the *per capita* birth rate (assumed to be unaffected by infection), b the *per capita* death rate in the absence of infection, and the total population is $N = X + Y_1 + Y_2$. It is assumed that both strains of the infection are lethal, so that, once infected, no hosts recover. This kind of model differs from conventional epidemiological ones in that the total host population is a dynamical variable, which may or may not be regulated to a stable equilibrium value by the infection; traditional studies (for example, Bailey, 1975) assume N to be a constant, determined by other factors. Despite their simplicity, equations of this general type have been shown to give a good fit to data for endemic infections that regulate experimental populations of laboratory mice (Anderson & May, 1979), and to give plausible explanations for the population dynamics of associations between foxes and rabies in Europe (Anderson, Jackson, May & Smith, 1981) and between various arthropods and viral or protozoan parasites (Anderson & May, 1981).

Analysing the system of equations (6)–(8), Levin & Pimentel (1981) showed that if one strain has significantly greater virulence in relation to its transmission advantage, it will not persist; conversely, if the pathogenicity α_1 is not significantly greater than α_2 while the transmission advantage is substantial (σ relatively large), the more virulent strain will win. For an intermediate range of the ratio α_1/α_2 in relation to the transmission advantage enjoyed by the more virulent strain, the two strains can co-exist.

Levin & Pimentel's (1981) study can be generalized in a variety of ways, and the essentials of their conclusions remain intact. Thus it is not necessary to assume that the more virulent strain can infect hosts bearing the less virulent strain, but that the reciprocal process is impossible; it is only necessary to assume that $\sigma\beta$ is the net excess of infections $2 \rightarrow 1$ over $1 \rightarrow 2$. The actual data for myxomatosis (see, for example, the work of Saunders, (1980)) suggest that individuals, once infected with one strain, do not acquire infection with another strain. Levin & Pimentel's general analysis can, however, be preserved by considering the more virulent strain (virulence α_1) to have a higher transmission rate, β_1 , than that, β_2 , of the less virulent strain (virulence α_2). In this case, if the disease is considered always to be lethal, the strain with the lower value of $(\alpha_1 + b)/\beta_1$ will always win. But if recovery is possible, or if other realistic complications are admitted, a range of coexistence is possible, corresponding to the two strains having roughly comparable values of the overall ratio between pathogenicity and transmissibility (Anderson & May, 1982a).

Bremermann (1980) has also used models of this type to examine the general way in which epidemiological parameters – such as transmission rate β , virulence α and recovery rate v – are likely to evolve in response to the selective pressures exerted on host and on parasite populations. As in all such studies of ‘evolutionarily stable strategies’ (ESS; Maynard Smith & Price, 1973), the underlying genetics is eschewed in pursuit of a more transparent but less rigorous analysis. Bremermann’s (1980) approach parallels that which we bring to bear on the myxomatosis-rabbit and other data, below.

Bremermann (1980) uses the basic set of equations introduced by Anderson & May (1979):

$$dX/dt = aN - bX - \beta XY + \gamma Z, \quad (9)$$

$$dY/dt = \beta XY - (\alpha + b + v) Y, \quad (10)$$

$$dZ/dt = vY - (b + \gamma) Z. \quad (11)$$

Here X , Y , Z are the number of susceptible, infected and recovered-and-immune hosts, respectively; $N = X + Y + Z$. The disease-induced mortality rate α , *per capita* birth rate a , disease-free mortality rate b , recovery rate v , and transmission rate β are all as defined previously, and γ is the rate of loss of immunity ($\gamma = 0$ if immunity is lifelong; $\gamma = \infty$ if there is no immunity, so that recovered individuals are again susceptible). This population grows exponentially at the rate $(a-b)$ in the absence of the disease. Once the disease becomes established, it will regulate the host population to a stable equilibrium if the virulence is sufficiently high (specifically if $\alpha > [a-b][1 + v/(b + \gamma)]$) and will slow the rate of exponential growth otherwise (Anderson & May, 1979). Following May & Anderson (1979), Bremermann (1980) observed that the fitness of the parasite is increased by having large β , and small α and v , whereas the host fitness is increased by having small β , small α and large v . Were these parameters not inextricably linked by the biological processes whereby virulence, recovery rate and production of transmission stages of the infective agent are intertwined, the ESS would clearly favour $\alpha \rightarrow 0$ (although the countervailing interests of host and parasites with regard to β and v would tend to drive them to some intermediate value, or into cycles). Insofar as there is a basis for the common view that ‘successful parasites and pathogens are harmless’, this is it. But the biologically based interlinkage among α , β and v invalidates this simple argument.

Bremermann (1980) explored some particular host-parasite systems, paying special attention to the role of polymorphism in maintaining immunological defenses. He was led, by this different route, to a central conclusion broadly similar to Hamilton’s, namely that the main reason for sexual reproduction is that, through recombination, it maintains polymorphisms which are ‘essential in preventing pathogens from adaptively breaking through immunological host resistance’ (Bremermann, 1980). In arriving at this conclusion, however, Bremermann used the mathematical models in a purely metaphorical way.

GENERAL DISCUSSION: BASIC REPRODUCTIVE RATE OF A PARASITE

An ambitious project is to meld the models described in the preceding two sections, to get sets of epidemiologically detailed equations like equations (6)–(11)

for each individual genotype of host interacting with each particular strain or genotype of parasite. Our preliminary studies suggest that the general conclusions to emerge from such a synthetic approach re-echo the theme sounded again and again in the diversity of models reviewed above: the winning parasite strain, or the possibility of coexistence of two or more strains, depends not simply on virulence alone but on the combination of virulence and transmissibility. But so long as we do not know the actual relations among the epidemiological parameters in any one real case, such studies tend to be unsatisfyingly abstract.

Turning back to the simple ESS-style model of equations (9)–(11), we note that the basic reproductive rate of the parasite (Anderson & May, 1981; Dietz, 1975, 1976; Yorke, Nathanson, Pianigiani & Martin, 1979) here is

$$R_0 = \frac{\beta N}{(\alpha + b + v)}. \quad (12)$$

Here β , α , b and v are as above, and N is the population density of the host (which may itself depend on the epidemiological parameters if the host population is regulated by the parasite). Host density, N , is assumed to be set by other ecological factors, and we further assume that the parasite is rapidly evolving compared to the host so that we focus just on equation (12). This latter assumption is discussed and examined in some detail by Hamilton (1980) and Levin *et al.* (1982). We see from equation (12) that the basic reproductive rate of the parasite would be maximized by $\alpha \rightarrow 0$ if α , v and β were not connected with each other. Conversely, if β was a faster than linear function of α , R_0 would be maximized by having α as large as possible; such pressures of individual selection on parasites would make for small populations of hosts and of parasites, providing a clear example where parasite group interests are at odds with individual selection.

We now proceed to examine the empirical patterns of relationship among these epidemiological parameters for some specific host–parasite associations.

MYXOMATOSIS IN AUSTRALIAN RABBITS

The myxoma virus was exceedingly virulent among populations of the rabbit *Oryctolagus cuniculus* in Australia when first introduced in 1950. As carefully documented by Fenner & Ratcliffe (1966), successively less virulent strains of the myxoma virus came to preponderate during the subsequent decade. At the same time, the rabbit populations in Australia exhibited increasing resistance, so that any characterization of the coevolutionary process in terms only of the Darwinian fitness of the parasite (along the lines laid down in the two preceding paragraphs) is a gross over-simplification. Nevertheless, we pursue this crude approximation to see to what extent the discussion based on equation (12) can give a consistent account of the observed facts. Our approach is greatly facilitated by the careful experimental protocol adopted by the virologists working with the myxoma virus, in which the virulence of field strains of the virus were tested against standard laboratory strains of the rabbit, and the susceptibility of wild rabbits was tested against defined laboratory strains of the virus.

Fenner & Ratcliffe (1966) divided the myxoma virus into 6 strains, according to grade of virulence. The basic data for the percentage mortality and mean survival time of those rabbits (a standard laboratory strain) that died rather than

Table 1. *Some epidemiological parameters for various grades of the myxoma virus in wild populations of rabbits in Australia*

Virus grade	Mean survival time, $1/\alpha$ (days)	Average case mortality (%)	Virulence, α (/day)	Recovery rate, v (/day)
I	11.0	99.9	0.091	0.0001
II	14.5	97.0	0.069	0.0022
IIIA	19.5	92.5	0.051	0.0042
IIIB	25.5	80.0	0.039	0.0100
IV	39.5	60.0	0.025	0.0169
V	118.0	22.5	0.008	0.0301

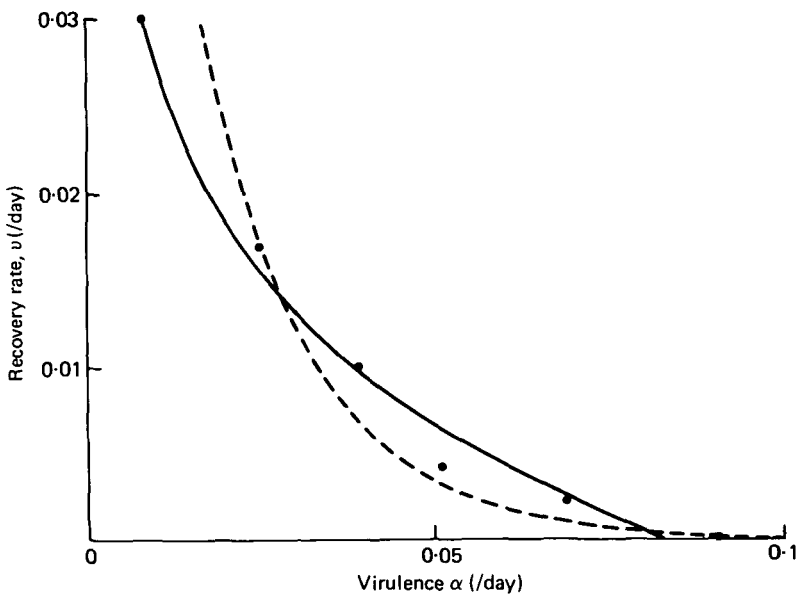


Fig. 1. The empirical relationship between virulence, α , and recovery rate, v , for various strains of myxoma virus in wild populations of rabbits in Australia. (●), Observed values (Table 1 and associated discussion in the text); (—) and (---) are the best fits with the functional forms of equations (13) and (14), respectively.

recovered are set out in Table 1, for each of these 6 strains of the virus. We ignore the details of the statistical distribution of mortalities and recoveries (which are discussed by Fenner & Ratcliffe (1966) and by Saunders (1980)), and instead simply assume a constant rate of disease-induced mortality α and a constant rate of recovery v . The proportion that die from infection is then $\alpha/(\alpha + v)$, which enables us to estimate the recovery rate v from the basic data given in the second and third columns of Table 1; the resulting estimate is set out as the final column in Table 1.

We see that the values of α and v for the various strains of the virus are inversely related. This empirical relation is displayed in Fig. 1. The solid curve illustrates the fit to the data obtained from the functional form

$$v(\alpha) = c + d \ln \alpha. \quad (13)$$

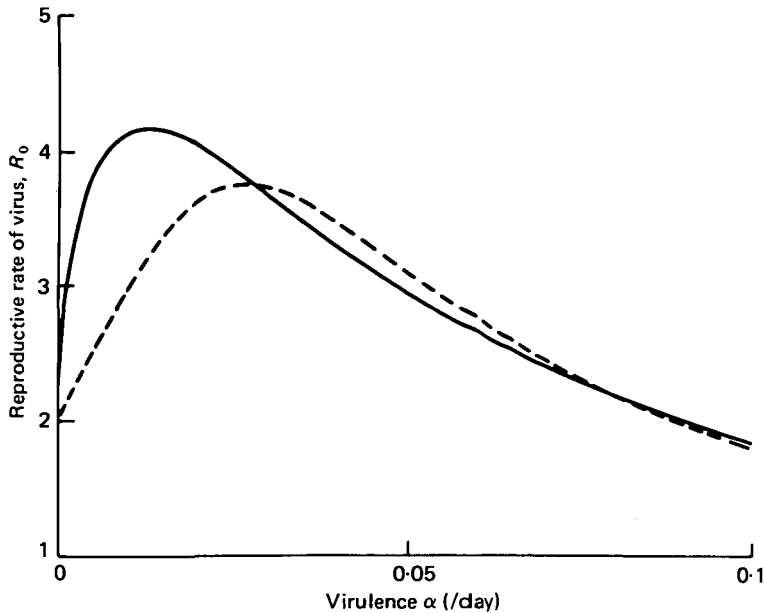


Fig. 2. The relationship between intrinsic reproductive rate, R_0 , and virulence, α , for the various strains of myxoma virus in wild populations of rabbits in Australia. Here R_0 is given by equation (12), the disease-free mortality rate b is 0.011/day and βN is arbitrarily set constant at 0.2/day. The relationship between recovery rate v and α is taken from Fig. 1; (—) and (---) correspond to the empirical relationships of equations (13) and (14) respectively.

With $c = -0.032$ and $d = -0.0129$ we have an excellent fit ($r^2 = 0.987$; $r = 0.993$). The dashed line shows the corresponding fit with the function

$$v(\alpha) = c \exp(-d\alpha). \quad (14)$$

With $c = 0.088$ and $d = 65.0$ the agreement is good ($r^2 = 0.910$; $r = 0.954$), although significantly less so than for equation (13). A power law of the form

$$v(\alpha) = c\alpha^d \quad (15)$$

gives at best a poor fit.

The results in Table 1 and Fig. 1 concern only the parameters α and v in equation (12), and provide no information about the transmission rate, β , as such. There is good qualitative evidence, however, that high virulence (grades I–III) is typically associated with lots of open lesions, and hence that mosquitoes (the vectors in Australia) or fleas (the vectors in Britain) can more easily bite infected wounds and acquire the virus. Low virulence (grades IV and V) is correspondingly associated with poor transmission. These tendencies for β to decrease with decreasing α (see, for example, figs 12 and 13 and table 3 in Fenner & Ratcliffe (1966)) are less pronounced than the inverse relationship between α and v , and are more difficult to quantify. We therefore initially make the additional rough approximation of taking β to be a constant, independent of α in equation (12).

Using the empirical relationship between α and v shown in Fig. 1, we can use equation (12) to plot the rough dependence of the intrinsic reproductive rate, R_0 ,

Table 2. Comparison of the virulence of field strains of myxoma virus in Great Britain, Australia and France (from Ross, 1982), contrasting initial frequencies with those several years after introduction

	Virulence grade (percentage occurrence)					
	I	II	III A	III B	IV	V
Great Britain						
1953	100	—	—	—	—	—
1962–1967	3.0	15.1	48.4	22.7	10.3	0.7
1968–1970	0	0	78.0	22.0	0	0
1971–1973	0	3.3	36.7	56.7	3.3	0
1974–1976	1.3	23.3	55.0	11.8	8.6	0
1977–1980	0	30.4	56.5	8.7	4.3	0
Australia						
1950–1951	100	—	—	—	—	—
1958–1959	0	25.0	29.0	27.0	14.0	5.0
1963–1964	0	0.3	26.0	34.0	31.3	8.3
France						
1953	100	—	—	—	—	—
1962	11.0	19.3	34.6	20.8	13.5	0.8
1968	2.0	4.1	14.4	20.7	58.8	4.3

of the various strains of myxoma virus as a function of virulence, α , for the Australian myxomatosis–rabbit system. This is done in Fig. 2; here we have put $b = 0.011/\text{day}$ (Fenner & Ratcliffe, 1965), and arbitrarily assigned $\beta N = 0.2/\text{day}$. R_0 is seen to attain its maximum value for an *intermediate* grade of virulence of the virus. Specifically, the virulence giving the maximum reproductive rate for the parasite (which can be obtained analytically from equation (12) as the value of α for which $dv/d\alpha = -1$) is $\alpha = 0.013/\text{day}$ for the empirical relation equation (13), or $\alpha = 0.027/\text{day}$ for the less satisfactory empirical relation equation (14). It is easy to get an intuitive understanding of why this intermediate grade of virulence may be best: too high an α kills off hosts too fast, diminishing their capacity to transmit the infection; but too low an α corresponds to a very quick recovery time, so that again transmission is relatively weak.

These conclusions can be compared with the observed facts about the relative frequencies of the various strains of myxoma virus within field populations of rabbits. When first introduced into Australia in 1950–51 the virus was of virulence grade I. There was at first rapid change, with increasing proportions of successively lower virulence grades. By the late 1950s and early 1960s, however, the relative frequencies of the different virulence grades had settled to roughly steady values (Fenner & Ratcliffe, 1966). These approximately steady proportions are set out in Table 2, which shows the virus apparently to have evolved to an intermediate degree of virulence centred around grades III A–III B–IV. This contrasts with our crude theoretical prediction, which on the basis of the empirical relation equation (13) suggests an equilibrium around grades IV–V (or an equilibrium around grade IV if the less accurate empirical relation equation (14) is used).

Table 2 also shows the distribution of frequencies of virulence grades to which the virus appears to have settled in wild populations of rabbits in Britain and France. The essential ecological difference among the myxomatosis–rabbit

associations in the three countries is that mosquitoes are the vectors in Australia and France, and fleas in Britain. Transmission by fleas is thought to be less efficient since the longer and larger mouth-parts of mosquitoes enable the latter vector to transmit lower virulence grades of the virus more effectively. This may explain the higher incidence of Grade IV strains in Australia and France (Ross, 1982).

As discussed above, there is some evidence to suggest that β also changes with the pathogenicity, α , of the virus (Mead-Briggs & Vaughan, 1975). There appears to be a curvilinear relationship between transmissibility and the average survival times of rabbits infected with the different virulence grades, with a maximum value of β at some intermediate value of α . This type of relationship would clearly have the effect of pushing the theoretically predicted grade of virulence closer to the observed grade around IIIB.

So far, we have only considered the evolutionary pressures acting on the virus. The disease quite clearly also acts as a strong selective pressure on the rabbit. This is manifest in Australia and Britain by the evolution of increasing resistance to the myxoma virus. Mean survival times of 'resistant' rabbits infected with a Grade IIIA strain (29–36 days) are significantly longer than those of fully susceptible laboratory rabbits (17–22 days). The evolution of resistance acts as a further selective pressure on the virus, tending to select for higher virulence grades of the virus (see Table 5, Fenner & Myers (1978)). This trend is particularly apparent in Britain and Australia where the available evidence suggests that resistant rabbits are evolving (Ross, 1982). Our neglect of the evolution of resistance among rabbits is a serious shortcoming in the above analysis, but quantitative data on the relative frequencies of 'resistant' types is limited at present.

In short, we are aware of the many serious deficiencies in the above analysis of the Australian and British data. Our justification for presenting the analysis is that it represents a first step beyond the purely abstract discussions that are characteristic of essentially all previous work in this general area.

BACTERIA AND LABORATORY MICE

The extensive laboratory investigations of Greenwood, Bradford Hill, Topley & Wilson, (1936) come tantalizingly close to allowing us to make analyses, similar to that presented above, for the association between mice and various bacterial and viral infections. Unfortunately, however, the data are not available in a form that permits us to extract empirical relationships among α , v and β for the various grades or strains of a particular bacterium or virus. Some qualitative patterns are nevertheless interesting (see also the discussion of the relationship between α and the equilibrium density of mouse populations regulated by such infections, in Anderson & May (1979)).

For mouse plague (*Pasteurella muris* in modern terminology: *P. muriseptica* in the usage current in 1936), there is qualitative indication that high virulence (large α) is associated with high infectivity (high transmission rate β) in populations of laboratory mice. This general trend is documented in Table XL of Greenwood *et al.* (1936) reproduced here as Table 3. We see that if the strains are graded in order of decreasing virulence (summed deaths over all doses), there is a rough correlation with the number of mice which contract the infection from the initial infectees,

Table 3. *Virulence and infectivity of various strains of Pasteurella muris in laboratory populations of mice*

Strain of <i>P. muris</i>	Virulence grade (proportion of deaths over all doses)	Infectivity (number acquiring infection out of 100 mice exposed)
P64	0.96	79
P62	0.80	62
PA39	0.80	13
P29	0.75	26
P58	0.20	19

under standard laboratory conditions. This rough correlation is, however, far from perfect.

For mouse typhoid (*Salmonella typhimurium* in modern terminology; *Bacteria aeortrycke* in 1936 usage), there is a similar rough correlation between the virulence of the various strains of the bacterium and their ability to spread within laboratory populations of mice (pp. 148–153 in Greenwood *et al.* (1936).

BACULOVIRUSES AND INSECTS

A striking example of an association between parasite virulence and transmission efficiency is that observed in interactions between nuclear polyhedrosis viruses and their Lepidopteran insect hosts (Anderson & May, 1981). These viruses, which belong to the group Baculoviridae, are directly transmitted between hosts by means of an inclusion body which contains virus particles. The replication cycle of the parasite within the insect is completed with the production of more occluded viruses which are released into the environment upon the death of the host. The number of infective stages released from a single host is invariably very large, being of the order of 10^6 – 10^8 inclusion bodies. Their rate of release into the environment of the host is clearly dependent on the rate at which the virus kills its host.

In the simplest case, where the net rate of production is directly proportional to the net death rate of infected hosts, the basic reproductive rate, R_0 , is

$$R_0 = (\bar{\beta}\lambda\alpha N)/[(\alpha + b + v)(\mu + \bar{\beta}N)]. \quad (16)$$

Here α , b , v and N are defined in equation (12), λ is the average number of infective stages released on the death of an infected host, $\bar{\beta}$ is the transmission rate of infective stages to the insect host and $1/\mu$ is the life-expectancy of the inclusion body in the external environment. The basic reproductive rate increases in value from zero (when $\alpha = 0$) to a maximum value of $\bar{\beta}\lambda N/(\mu + \bar{\beta}N)$ as $\alpha \rightarrow \infty$.

A refinement to this simple example results from the observation that in most associations there is a trade off between the number of inclusion bodies produced by the virus and the life-span of an infected insect. If an infected host dies too rapidly then insufficient time will have elapsed for the production of the maximum number of transmission stages permitted by the available resources within the host. If, as appears likely, the value of λ rises to some asymptote as infected host life-span increases then the value of the basic reproductive rate, R_0 ,

will rise (from $R_0 = 0$) to a maximum and then decay back to zero as the pathogenicity of the virus increases. In other words, the reproductive success of the parasite will be maximal at some intermediate level of virulence.

A different, but closely related group of insect viruses (also belonging to the Baculoviridae), the cytoplasmic polyhedrosis viruses, have evolved a slightly different reproductive strategy. In contrast to the nuclear polyhedrosis virus, they are not necessarily reliant on the death of the host for the release of transmission stages, but produce and release inclusion bodies throughout the duration of host infection. Interestingly, cytoplasmic polyhedrosis viruses are less pathogenic to their insect hosts than the nuclear polyhedrosis group.

CONCLUSIONS

We have first presented a review of some of the wide range of mathematical models that are being used to explore the coevolution of hosts and parasites. Some of these models take explicit account of the genetics of the interacting populations, but treat epidemiological aspects crudely or not at all; others give attention to density-dependent and epidemiological factors, without explicit consideration of the population genetics; yet other models represent forms of compromise between these extremes. Essentially all these studies emphasize that coevolution between hosts and parasites (defined to include viruses, bacteria, protozoans and helminths) may explain much of the polymorphism found in natural populations. More specifically, most of these diverse studies concur in finding that the maintenance of a particular strain or genotype of parasite, or the coexistence of different strains, depends not only on their virulence but also on factors influencing their overall transmissibility. These formal studies make it clear that the coevolutionary trajectory followed by any particular host-parasite association will ultimately depend on the way the virulence and the production of transmission stages of the parasite are linked together: depending on the specifics of this linkage, the coevolutionary course can be toward essentially zero virulence, or to very high virulence, or to some intermediate grade.

In the second part of the paper, we have tried to find empirical information bearing on the interlinkage between virulence and transmission parameters in real systems. The best-documented example seems to be the introduction of myxomatosis in wild populations of rabbits in Australia. Using quantitative data for the relation between virulence and transmission parameters for various strains of the myxoma virus, we show that a crude kind of ESS model leads to conclusions qualitatively in agreement with the observed course of evolution in this host-parasite association; here the system appears to have settled to one in which the preponderant strains of the virus are those of intermediate virulence.

Our major conclusion is that a 'well-balanced' host-parasite association is *not necessarily* one in which the parasite does little harm to its host. Four principal observations support this view. *First*, as emphasized in this paper, transmission efficiency, and hence reproductive success, is often positively correlated (up to a certain level) with parasite virulence or pathogenicity. *Second*, the parasitic mode of life is the most commonly adopted of all modes of life in the animal kingdom. This observation is to be compared with the comparative rarity of amensal or commensal associations; the evolutionary end point suggested by conventional

dogma. *Third*, the extreme polymorphism in natural populations of animals of the genetic systems which control specific and non-specific host responses to parasitic invasion. It appears likely that this diversity is a result of continual selection by a very wide variety of parasite species and strains. *Fourth*, and finally, it is difficult to accept that the observed sophistication and complexity of vertebrate and invertebrate immune systems would have evolved, and been maintained, if parasites were not, and are not, of major importance to the fitness of animal species. When confronted by this sophistication the parasite is constantly battling to survive. The ability to multiply rapidly within the host, or produce large numbers of transmission stages (both attributes frequently being correlated with parasite pathogenicity) will often be beneficial to reproductive success even if the host is eventually killed by such action.

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