

# POPULATIONS AND INFECTIOUS DISEASES: ECOLOGY OR EPIDEMIOLOGY?

## THE EIGHTH TANSLEY LECTURE\*

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### INTRODUCTION

As someone trained in a University department in which ecology and parasitology were subjects of research specialization, it is perhaps hardly surprising that I acquired an interest in parasite ecology as a young student. In the 1960s and 1970s, research in this area was more closely linked to the prevailing concepts and fashions in the discipline of parasitology, as opposed to those in ecology. However, the growth in ecological research during the 1970s began to influence thinking about the parasitic mode of life and, slowly, concepts such as the crowding effect (Read 1950), parasite overdispersion (Crofton 1971) and host specificity (Noble & Noble 1976) in parasitology, began to be linked to the more developed ideas in ecology concerning the significances of density dependence, spatial heterogeneity and reproductive strategies in determining the distribution and abundance of plant and animal species (Krebs 1978; Southwood 1976; Varley, Gradwell & Hassell 1973; May 1975; Hutchinson 1978). More recently, there has been an encouraging trend for convergence in the concepts employed by ecologists in thinking about the transmission and persistence of infectious agents in natural or managed plant and animal communities, and those employed by epidemiologists concerned with the study of infection and disease in human communities (Anderson & Thresh 1988). The similarity in the population-based theories that underpin the disciplines of ecology and epidemiology, is the central theme of this paper.

Both disciplines have a lot to teach, and a lot to learn from each other. In modern ecology, for example, there is the tradition of developing simple mathematical models of population change to guide interpretation and parameter estimation. This approach is of great relevance in epidemiological study, where past traditions have centred more on pattern description and discrimination via the use of statistical methodologies (Kahn 1983). The mathematical theory of epidemic processes has been the subject of much research (Bailey 1975) but, sadly, this field has tended to be rather divorced from the constraints of data and from the necessity to compare prediction with observation. This well-developed area of applied mathematics has therefore had little impact, until very recently, on public health policy, the collection of data, or the development of epidemiological concepts. This is a great pity, as one of the major lessons epidemiology can teach ecology is the value of long-term data records of changes in organism abundance. Such data provides an excellent template against which to test ideas concerning the factors that determine population size. Epidemiological information is often acquired via national reporting systems which attempt to compile temporal trends in the incidences of important infections and diseases. An example is portrayed in Fig. 1,

\* Based on the biennial Tansley lecture of the British Ecological Society, given at Swansea on 20 December 1989.



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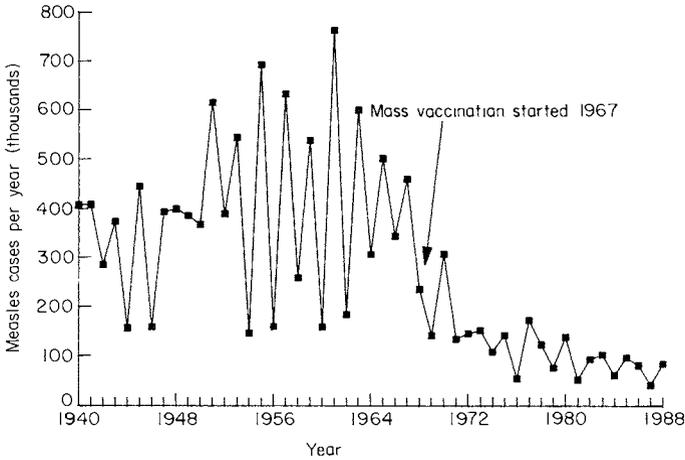


FIG. 1. The incidence of measles (reported cases per year) in England and Wales 1940–88. Mass immunization was introduced in 1967.

which records fluctuations in reported cases of measles (a viral infection) in England and Wales over the period 1940–88.

National epidemiological surveillance systems also capture what may be termed ‘large-scale experiments’ in population perturbation induced by the introduction of control measures such as mass vaccination, as illustrated in Fig. 1. It is hardly necessary to say that the motives for introducing mass vaccination are not associated with the desire to monitor population fluctuation following a perturbation. However, the data serves as a valuable record of the impact of a reduction in the reproductive potential of a parasite on its distribution and abundance within its host population. In addition, it is often possible to link changes in the abundance of the infectious agent, with changes in the abundance of its host. For example, in the case of measles, data on infection can be compared with precise information on human population size and net birth and death rates in England

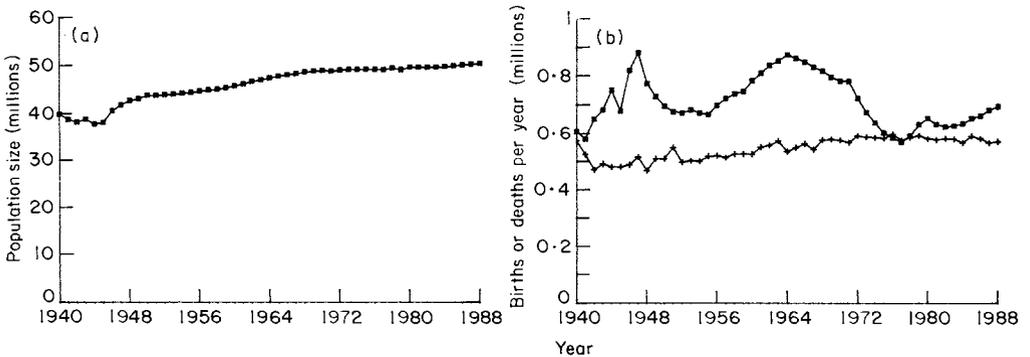


FIG. 2. Temporal trends over the period 1940–88 in (a) population size, and (b) net birth rate (■) and net death rate (+) in England and Wales.

and Wales (Fig. 2). Demographic factors remained fairly constant over the 1940–88 period and, hence, observed changes in the incidence of infection from 1967 onwards can be interpreted as a direct consequence of the impact of mass vaccination.

It is rare in ecological study that such long-term and detailed records are available of fluctuation in the abundances of two interacting species. The epidemiological literature therefore provides a rich source of information for testing a wide variety of ecological concepts. The measles records, for example, provide an excellent example of simple oscillations within a two-species interaction. In the period 1951–67, measles exhibits recurrent epidemic behaviour with a 2-year period between major epidemics. Theoretical prediction, based on a simple Lotka–Volterra model, are in good agreement with observation (Anderson & May 1982; Anderson, Grenfell & May 1984).

An important area in which ecologists can benefit from the experience and techniques of epidemiologists concerns the study of genetic change concomitant with changes in population abundance. The fields of population ecology and population genetics remain somewhat distinct at present, both in the development of theory and in field study design. The very nature of the parasitic mode of life, however, implies that pathogens and hosts coevolve in a very dynamic way, and hence epidemiologists have had to devise methods for assessing the genetic structure of pathogen population and its relationship with observed patterns of transmission and disease. One of the best known examples is that of the human influenza virus. Viral strains are classified on the basis of very labile surface haemagglutinin (H) and neuraminidase (N) antigens, which undergo infrequent major ‘shifts’ (e.g. from  $H_1$  to  $H_2$ , and from  $N_1$  to  $N_2$ ; infection by one strain confers little immunity to infection by another strain) and more frequent minor ‘drifts’. Major ‘shifts’ facilitate virus persistence in a population with a high degree of herd immunity to earlier antigenic variants, and are often associated with significant changes in the severity of disease induced by infection. The detection of genetic change requires biochemical, molecular and immunological methods which, today, provide great precision in certain areas. The polymerase chain reaction (PCR) technique, for example, is capable of detecting and amplifying extremely small quantities of a particular nucleotide sequence. These tools are not widely used in ecological research at present, but they do offer enhanced precision in future work on population biology and population genetics.

With the aim of illustrating how concepts and methods in ecology can help in epidemiological study, and vice versa, the paper is organized into five sections, each focusing on a particular topic. The first considers the role of infectious agents in the regulation of host abundance, one topical example being the potential demographic impact of the acquired immunodeficiency syndrome (AIDS) in human communities. The second section examines one of the major themes in current ecological research, namely the role of various kinds of heterogeneity in determining population abundance. Particular emphasis is placed on the significance of behavioural factors in the transmission of infection. The third section takes a more applied slant in examining the ecological concepts that underpin the design and implementation of programmes for the control of infection and disease. The fourth section considers how an understanding of the transmission dynamics of infectious agents helps us in assessing the persistence properties of genetically modified bacteria, where plasmids are the vehicles of the transference of genetic material. The fifth and final section moves down a level of organization to examine a relatively new area of research; namely, the population ecology of the immune system. The paper ends with a brief discussion of the major themes emerging from consideration of these five topics.

## ROLE OF INFECTIOUS DISEASES IN HOST POPULATION REGULATION

In the ecological literature there has been a tendency to view infectious agents in terms of epidemics which suddenly arise, sweep through a host population and then disappear as if by magic. The literature contains many descriptions of such phenomena within human, animal and plant populations. This view naturally gives rise to the belief that infectious disease agents (or parasites) act as rather erratic or unpredictable factors in the regulation of host population growth. In recent years, however, a body of theory has been developed which, in conjunction with experimental work and observation in natural habitats, has provided a rather different view of the regulatory potential of infectious agents (Anderson 1979; Anderson & May 1979; May & Anderson 1979). This section highlights a few of the major features of this research by reference to a number of topical examples.

Whether or not a particular infectious agent is able to persist in a defined host population depends on the magnitude of its basic reproductive rate,  $R_0$ , which defines the average number of secondary cases of infection (or production of sexually mature parasites) produced by one primary case (or mature female parasite) in a susceptible population of defined density. The quantity  $R_0$  measures the transmission potential of the infectious diseases and is defined in terms of parameters associated with the typical course of infection in the host and certain demographic features of the host population. For example, in the case of a directly transmitted microparasite (e.g. virus or bacteria) which is not transmitted vertically (i.e. from mother to offspring),  $R_0$  may be defined as:

$$R_0 = \beta X / (\alpha + b + \sigma) \quad (1)$$

Where  $X$  denotes the density of hosts,  $\beta$  is the probability of transmission per contact between susceptible and infected hosts (analogous to the parameter for searching efficiency in models of predator-prey and host-parasitoid interactions),  $\alpha$  is the disease-induced mortality rate,  $b$  is the per capita mortality rate of uninfected hosts, and  $\sigma$  is the rate of recovery from infection (see Anderson 1979). For persistence,  $R_0$  must exceed unity in value ( $R_0 > 1$ ). Alternatively, eqn (1) can be expressed in the form

$$X > X_T = (\alpha + b + \sigma) / \beta \quad (2)$$

where  $X_T$  denotes the critical host density for disease persistence. Equation (1) introduces two concepts. The first is that persistence is dependent on a few parameters that measure host and parasite characteristics. The second is the requirement that the density of susceptible hosts exceeds some critical value for persistence and spread (Anderson, 1990).

If persistence is ensured (i.e.  $R_0 > 1$ ), whether or not the parasite is able to regulate host abundance (in the absence of other constraints) depends on the degree to which the infectious agent increases host mortality (or reduces fecundity). In the simplest case of a directly transmitted virus which only influences host mortality, the requirement for regulation is

$$\alpha > r[1 + \sigma/(b + \gamma)] \quad (3)$$

where  $r$  is the intrinsic growth rate of the host and  $1/\gamma$  records the duration of immunity to reinfection in those hosts that recover from primary infection. Regulation is more easily achieved if the infection reduces reproduction and survival, such that in the limit where infected hosts do not reproduce, regulation is always assured. If eqn (3) is not satisfied but  $R_0 > 1$ , the host population will grow exponentially, but at a reduced rate  $\rho$  ( $\rho < r$ ) where in the simple case of the directly transmitted virus

$$\rho \approx r - \alpha[1 + \sigma/(b + \gamma)] \quad (4)$$

In these circumstances the proportion of infected hosts will settle to a constant value in the exponentially growing host population (Anderson 1979).

When regulation occurs, the host population may settle to a stable point or the infection may induce oscillatory fluctuations in host and pathogen abundance. A good illustration of this point is provided by the rabies virus and its impact on red fox (*Vulpes vulpes*) populations in Europe (Anderson *et al.* 1981). Red foxes typically exist at densities in the range of  $< 1\text{--}10$  animals  $\text{km}^{-2}$  in many European countries where the intrinsic growth rate,  $r$ , is of the order of  $0.5 \text{ year}^{-1}$ . Infection with the rabies virus is normally fatal with death occurring, on average, about 30–40 days following infection. A simple model of this interaction suggests that at high habitat carrying capacities (of the order of  $5\text{--}10$  animals  $\text{km}^{-2}$ ) the virus will significantly depress host dependence and induce oscillatory fluctuations in host and pathogen abundance. A numerical simulation is presented in Fig. 3, which records fluctuations in total fox population density and the percentage of rabid animals over a 20-year time span. In this example, in the absence of infection the fox population would settle to its disease-free density (habitat carrying capacity) of 10 animals  $\text{km}^{-2}$ . As a consequence of its high pathogenicity (all infected animals die) the virus is able to significantly depress fox abundance from the disease-free carrying capacity and to induce 4-year cycles in host density. Also note that the prevalence of rabid animals peaks just after the peak in fox density. However, of greatest interest is the prediction that host population regulation, and significant depression of host density, can be induced even though only a small fraction of animals are rabid during an epidemic outbreak of the disease (i.e. 5%).

Over long periods of time the selective pressure applied by rabies is likely to favour genetic strains of the fox population that are able to recover from infection and develop some degree of immunity to reinfection. In Europe and North Africa there is some evidence to suggest that resistant strains of the host are beginning to appear, i.e. foxes with antibodies to virus antigens but no symptoms of disease. The criteria for population

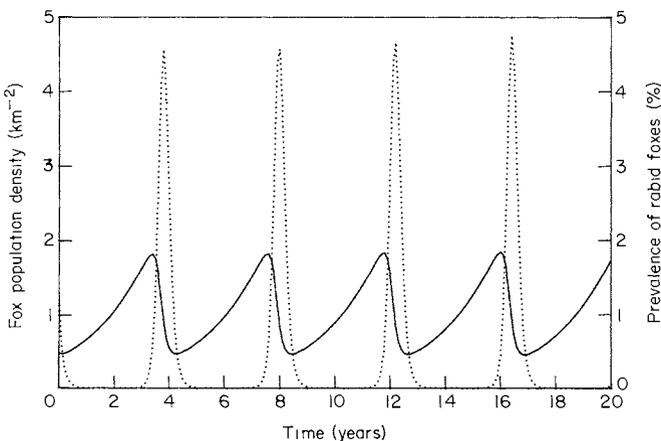


FIG. 3. Oscillatory fluctuations in total fox population density and the density of rabid foxes generated by a simple model of the interaction between the rabies virus and its host population (see Anderson *et al.* 1981). Parameter values; disease-free carrying capacity,  $10 \text{ km}^2$ ,  $r = 0.5 \text{ year}^{-1}$ ,  $\beta = 80 \text{ year}^{-1}$ ,  $\sigma = 13 \text{ year}^{-1}$ ,  $\alpha = 73 \text{ year}^{-1}$ .

regulation defined in eqn (3) suggests that a few biological properties of the interaction determine the regulatory ability of the pathogen. For short-lived host species, such as insects with high reproductive potentials, regulation will only result if the parasite is highly pathogenic such that few hosts recover from infection. Acquired immunity in such species is usually absent, so that recovery from infection ( $\sigma$ ) is the major determinant of regulatory impact. In the case of vertebrate species, however, with sophisticated immunological defences, the duration of acquired immunity ( $1/\gamma$ ) plus the ability to recover ( $\sigma$ ) are the major determinants. An illustration of this point is presented in Fig. 4 for the fox-rabies virus interaction. In this figure the boundary between pathogen-regulated and pathogen-unregulated host population growth is plotted as a function of the fraction of foxes who manage to recover from infection and the duration of acquired immunity in those that recover (eqn (3)). Note that the fox population is only able to 'escape' from the regulatory impact of rabies provided a high fraction are able to recover. This example highlights the point that for long-lived species with low population growth rates, the evolution of an effective immune system that enables infected individuals to recover and resist reinfection, is central to population survival in the face of continual exposure to a wide range of infectious agents.

The human species provides a further example in this context. Consider, for instance, the impact of a viral infection such as smallpox (now eradicated worldwide; see Fenner *et al.* 1988) in a developing country with a 4% growth rate per annum ( $r=0.04$ ) in the absence of infection. With an average duration of infection of 2 weeks and a 50% case fatality rate, eqn (3) suggests that the virus would be unable to regulate human population growth, given that immunity in those who recover appears to be lifelong.

The current pandemic of AIDS, induced by the human immunodeficiency virus type 1 (HIV-1) presents a rather different problem to that of smallpox. The infection appears to induce disease in a very high fraction of those infected with the virus and, once AIDS is diagnosed, life expectancy is of the order of 1 year in untreated persons. The time interval

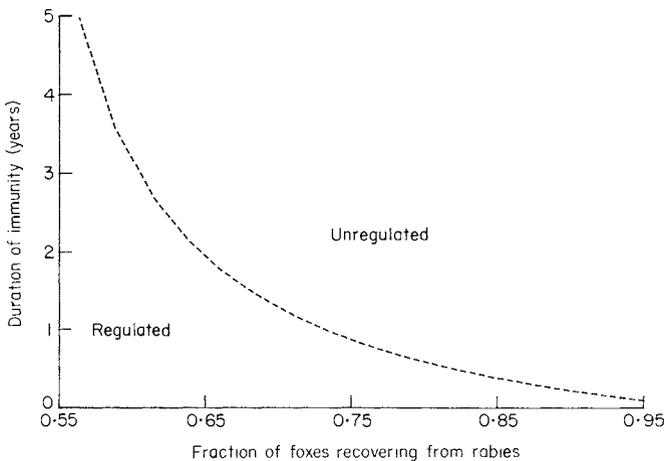


FIG. 4. The boundary between areas of parameter space that result in the rabies virus regulating fox density and areas in which the virus is unable to regulate host population growth, as predicted by eqn (3) in the main text. The parameters space depicted is that created by the duration of immunity ( $1/\gamma$ ) and the fraction of foxes who recover from infection,  $f$ , where  $f = \sigma/(\sigma + b + \alpha)$ .

from infection to the diagnosis of AIDS appears to be long: *c.* 10 years in sexually active adults. Throughout this long (and variable) incubation period an infected person may transmit the virus to a susceptible sexual partner. In addition, babies born to mothers who carry the virus have a high probability of acquiring infection (20–50%). Recent analyses of the potential demographic impact of AIDS on human population growth suggest that the disease could, under certain circumstances, reverse the sign of human population growth rates in developing countries (Anderson, May & McLean 1988; May, Anderson & McLean 1988a, b). In very simple models of the interaction between HIV-1 and human population growth, the asymptomatic growth rate,  $\rho$ , of the host population is given by

$$\rho = -(\mu + \alpha) + [ev(\Lambda + \mu + \alpha)]/[\Lambda - r + ev] \quad (5)$$

where  $\Lambda = \beta c - (\mu + \alpha)$ . Here  $\mu$  is the per capita mortality rate of uninfecteds,  $\alpha$  is the mortality rate of infecteds,  $\beta$  is the probability of transmission (per sexual partner),  $c$  is the effective rate of acquiring new sexual partner,  $(1 - \varepsilon)$  is fraction of babies born to infected mothers who acquire the infection (and die rapidly after birth), and  $r$  is the intrinsic growth rate of the human population.

Over the past year, very complex models of the interaction have been developed to assess potential demographic impact (see Anderson 1989; Anderson *et al.* 1989b). These models incorporate age dependency in human mortality and fertility, heterogeneity in sexual activity, distributed infectious and incubation periods, age dependency in sexual activity, unequal transmission probabilities for males and females, and heterogeneity in sexual contact between age-classes and sexual activity groups. Numerical studies of these more complex models, for plausible ranges of parameter values, suggest similar conclusions to those derived from simple models, namely, that HIV-1 may be able to reverse the sign of population growth rates in certain developing countries (1–4% growth rates prior to the introduction of HIV-1). The time-scale on which AIDS is likely to cause a population decline is predicted to be long, of the order of a few to many decades from the introduction of the virus. Demographic impact is enhanced by unequal transmission probabilities (higher from males to females than vice versa), high rates of sexual partner change in young sexually active adults and, on average, males having sexual contact with females younger than themselves. Impact is reduced if there is marked heterogeneity in rates of sexual partner change. At present, it is difficult to make precise statements concerning likely demographic impact in particular countries due to the paucity of data on patterns of sexual behaviour and the rate of spread of the virus in defined cohorts of people. However, the evidence that is emerging from certain countries in Sub-Saharan Africa, concerning the degree to which HIV-1 has penetrated urban and rural populations, suggests that the more pessimistic conclusions concerning demographic impact may come true in certain communities over the coming decades.

An illustration of the use of complex models of HIV transmission to assess the demographic impact of AIDS is presented in Fig. 5 (see Anderson 1989; Anderson *et al.* 1989b). The simulation records temporal changes in total population size, stratified by age, following the introduction of HIV-1 (at time  $t=0$  into a population of 16.6 million people with a 3.8% annual growth rate prior to the introduction). The graph also depicts time- and age-related changes in the number of people with AIDS. In this particular example, the chosen parameter values result in the disease being able to reverse the sign of the population growth rate approximately 30–40 years after the introduction of HIV-1. It is also interesting to note the predicted age distribution of AIDS cases, with peaks in infants due to vertical transmission, and in adults due to horizontal (=sexual)

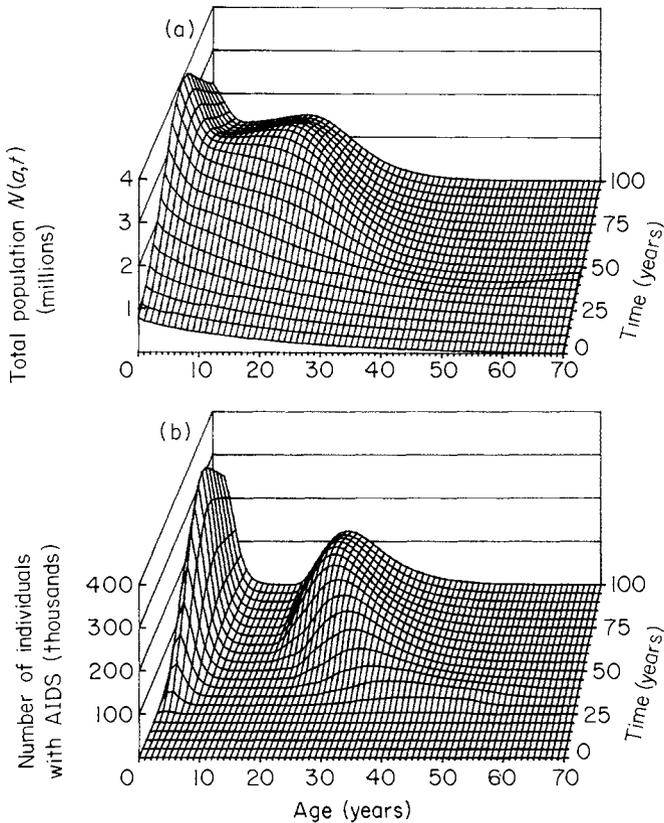


FIG. 5. The demographic impact of AIDS on human population growth and age structure as predicted by a simple model of the transmission dynamics of HIV-1 and human demography (see Anderson *et al.* 1989b). (a) Time-dependent changes in the age-structure of the human community following the introduction of HIV-1 at time  $t=0$  (at  $t=0$ , total population size was set at 16.6 million with a 3.8% annual growth rate). (b) Changes in the age distribution of people with AIDS as the epidemic develops through time. Note the peaks of disease in infants (vertical transmission) and in sexually active adults (horizontal transmission).

transmission. These predicted patterns in cases of disease are similar to those currently recorded in many African countries (Fig. 6).

Lentiviruses similar to HIV-1 have now been isolated from many species of primates from the continent of Africa. These viruses are collectively called simian immunodeficiency viruses (SIVs) and they represent the closest known relatives to HIV (Desrosiers, Daniel Li 1989). It has been suggested that human AIDS retroviruses originated from non-human primates in Africa (Kanki, Alroy & Essex 1985). For example, Peeters *et al.* (1989) recently reported the isolation of a retrovirus antigenically related to HIV-1 in two wild-born chimpanzees in Gabon. The apparent widespread occurrence of these viruses in natural populations of non-human primates raises the question of their likely demographic or regulatory impact on their host populations. Equation (5) provides some guidance on this issue. Birth ( $a$ ) and death ( $\mu$ ) rates of mammalian species appear to be linked by a simple power law relationship of the form  $a = g\mu^h$  where  $g$  and  $h$  are constants,

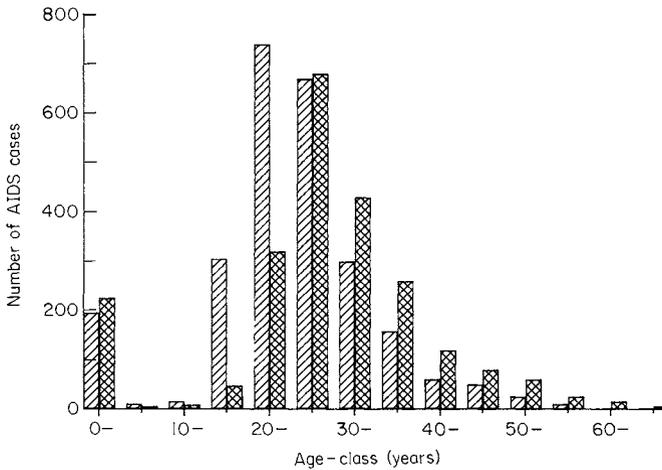


FIG. 6. Age and sex (females  $\square$ , and males  $\boxtimes$ ) distribution of AIDS cases reported in Uganda by the end of July 1988 (Berkley, Okware & Naamara 1989).

with approximate values of 0.9824 and 1.84, respectively (see Southwood (1981) and references therein). We can therefore express the intrinsic growth rate  $r$  in eqn (5) in terms of the death rate  $\mu$ . If we then assume fixed values for the rate of transmission of the virus ( $\beta c$ ), its pathogenicity ( $\alpha$ ), the efficiency of vertical transmission ( $1 - \epsilon$ ) and the duration of infection ( $1/v$ ), it is possible to plot the predicted asymptotic growth rate,  $\rho$ , of the primate population as a function of host life expectancy in the absence of infection ( $1/\mu$ ). This is done in Fig. 7 from which it can be seen that a lentivirus with given characteristics ( $1/\alpha = 1$  year,  $1/v = 10$  years) is less likely to be able to significantly depress population growth rates of primates such as the chimpanzee when compared with humans. This analysis is very simplistic, but it serves to illustrate the general point that infections that do not

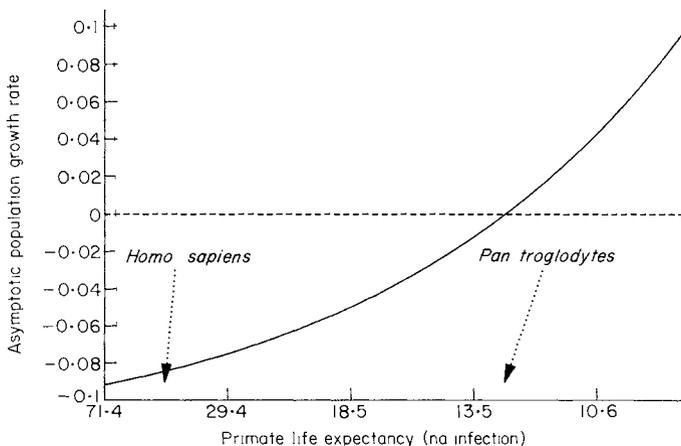


FIG. 7. The relationship between the asymptotic population growth rate in a primate population infected with an immunodeficiency virus (SIV or HIV) and the life expectancy of the primate host in the absence of infection as predicted by eqn (5) in the main text. See text for details.

induce immunity, and from which few hosts recover, are less able to regulate host species with high intrinsic growth rates than species with low growth rates. It also suggests that we cannot assume that a long-term relationship between lentiviruses and non-human primates implies that the population growth of human communities will not be affected significantly by the pandemic of HIV-1 in the coming decades.

## HETEROGENEITY IN HOST-PARASITE INTERACTIONS

One of the pervading themes in ecological research today is the significance of heterogeneity, whether spatial, genetic or behavioural, in determining the stability and resilience of species interactions (Hassell & May 1974; Anderson & May 1978; Chesson 1981; Lawton 1989; Walker 1989; Law & Watkinson 1989; Hassell & Anderson 1989). Within host-parasite association, non-random distributions of parasite numbers per host play a central role in determining patterns of infection and disease, plus the regulatory potential of the parasite.

Many factors can generate aggregation, including host and parasite genetics, host nutrition, host behaviour, acquired immunity and spatial factors. A comprehensive discussion of these is beyond the scope of this paper and this section simply highlights a few examples of their more striking effects on the distribution and abundance of host and infectious agents.

### Regulation of host abundance

One of the most striking features of observed distributions of parasite numbers per host is the degree of aggregation exhibited. Typically, most hosts harbour few parasites and a few harbour many (Fig. 8). The negative binomial distribution often provides a good empirical description of observed trends where the parameter,  $k$ , which inversely measures the degree of aggregation, adopts very low values (e.g. typically in the range 0.05–0.8). Interestingly, studies of helminth infection in humans and domestic animals suggest that those hosts with high levels of infection are predisposed to this state (see final

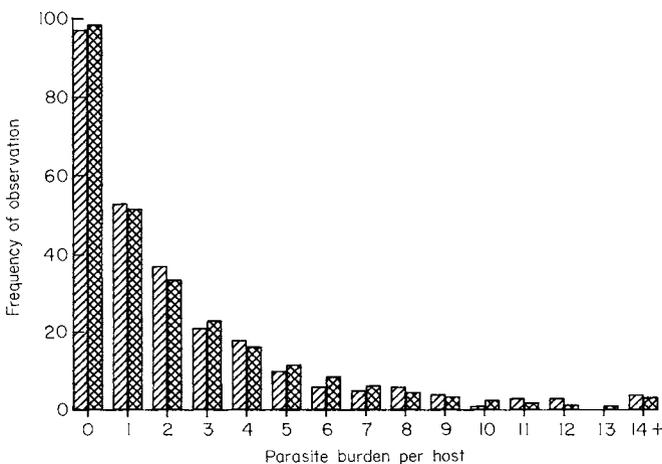


FIG. 8. Observed (▨) and expected (▩) frequency distribution of *Diclidophora denticulata* (monogenea) in the fish host *Gadus virens* and the best-fit negative binomial distribution ( $m = 2.28$ ,  $k = 0.684$ ) (Frankland 1954).

section and Fig. 37). Predisposition is thought to arise from a combination of genetic, spatial and behavioural factors (Bundy 1988; Haswell-Elkins, Elkins & Anderson 1987).

In the context of host population regulation by macroparasites, simple models of the population dynamics provide a clear picture of the significance of the degree of parasite aggregation to the stability of the association (Anderson & May 1978; May & Anderson 1978). The central biological feature of these associations is that parasite host mortality, or reduction in host fecundity, is positively correlated with parasite burden. Thus, in the case of mortality, the death of a few heavily infected hosts tends to result in the death of a large number of parasites. This effect tends to reduce the impact of the parasite on host abundance, as the degree of aggregation increases ( $k \rightarrow 0$ ). However, at the opposite extreme, the heavy mortality induced by randomly distributed parasites tends to induce unstable oscillations in host and parasite abundance. Hence aggregation appears stabilizing, with the caveat that if it is too extreme the parasite's impact on host mortality or fecundity will be too low to result in regulation of host abundance. These points are illustrated graphically in Fig. 9 which records host equilibrium density,  $H^*$ , as a function of the degree of aggregation (measured inversely by the negative binomial parameter  $k$ ) as predicted by a simple model of the interaction between a vertebrate host and a direct life cycle macroparasite (see Anderson & May 1978).

In most natural host-parasite interactions it appears probable that host genetic factors, which control innate susceptibility to infection or immunological responsiveness to parasite invasion, determine, to a large extent, the degree of observed parasite aggregation. Laboratory studies, for example, illustrate that random distributions of parasites can be generated in inbred laboratory mice exposed to a constant number of infective stages, while aggregated distributions are induced under the same experimental conditions in outbred laboratory mice (Crombie & Anderson 1985). However, spatial factors that determine host exposure to infection are also often important (Keymer & Anderson 1979). The interplay between ecological factors, and host and parasite genetics, in determining observed patterns of parasite distribution is an interesting area for further research.

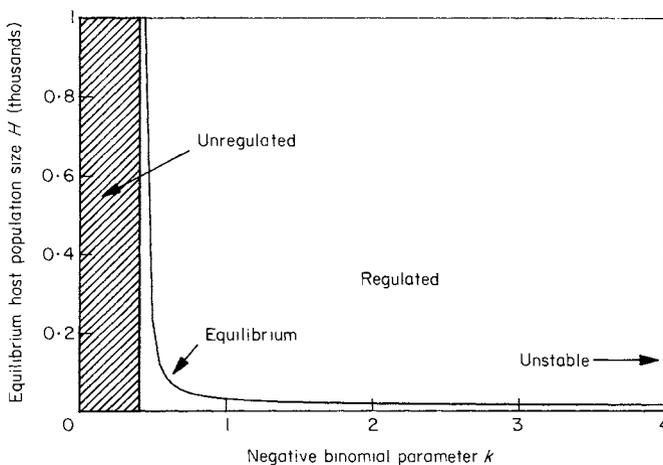


FIG. 9. Host equilibrium density,  $H$ , as a function of the degree of parasite aggregation (measured inversely by the negative binomial parameter,  $k$ ) as predicted by a simple model of a direct life cycle macroparasite (Anderson & May 1978).

*Host behaviour*

The transition of most, if not all, infectious agents is influenced to a lesser or greater degree by host behaviour. Heterogeneity in such behaviour can have a marked influence on the pattern of infection observed in any given host community. An interesting example of its influence is provided by sexually transmitted infections, such as the human immunodeficiency virus type 1 (HIV-1). The prevailing pattern of sexual behaviour in a host community is one of the major determinants of the degree to which infection will spread and the impact it has on host population size.

As a consequence of the current pandemic of AIDS, much recent epidemiological research has focused on the quantification of patterns of sexual behaviour in defined human communities (or risk groups such as male homosexuals or heterosexuals). This is a difficult area to study, given the obvious problems surrounding the representativeness of a given sample drawn from a defined population and the truthfulness of responses to questions about the intimate details of an individual's sexual behaviour (Anderson & Johnson 1989; Johnson *et al.* 1989; Konings *et al.* 1989).

In such surveys, questions have tended to focus on rates of sexual partner change, and the frequency plus type of sexual activity. An example of the heterogeneity recorded in one such study based on a blanket survey (confidential, anonymous completion of questionnaire) of undergraduates attending a particular course in a U.K. university is recorded in Fig. 10. The survey recorded the number of different sexual partners over various time intervals (1 month to lifetime) and shows that the variance to mean ratio of sex partners per unit of time varies from underdispersed over short time intervals (1 month), to highly overdispersed over long time intervals (5 years) (Anderson 1988). A larger pilot survey based on random sampling of the general population in 1989, which forms part of a planned national survey in England and Wales, produced similar results as recorded in Fig. 11. In this figure two variables, stratified by sex, are recorded: (a) sex acts over the past 7 days (Johnson *et al.* 1989), and (b) sexual partners over the past year. The

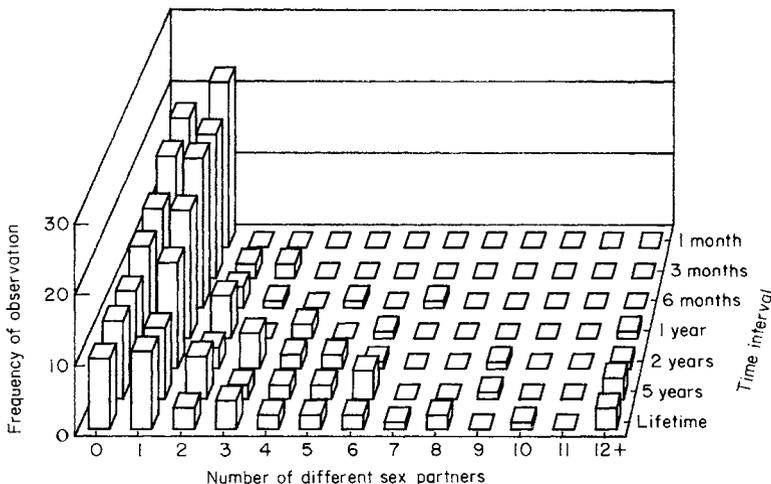


FIG. 10. Frequency distributions of claimed number of different sexual partners over varying time periods (1 month–lifetime) recorded in a survey of male and female students in 1987 (see text for details).

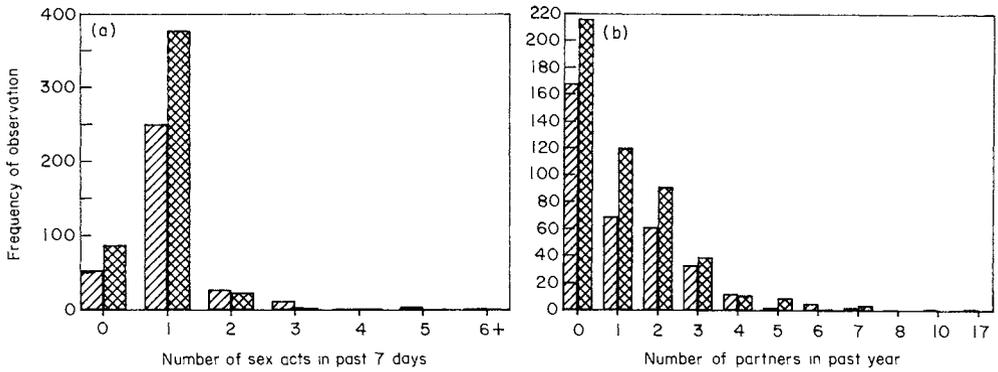


FIG. 11. (a) Frequency distributions of the number of sex acts in the past 7 days and (b) the number of different sexual partners over the past year for males (▨) and females (▩), in a sample of approximately 1000 heterosexuals drawn from the adult population of England and Wales in 1988–89 (see Johnson *et al.* 1989).

recorded association is plotted for males in Fig. 12. Interestingly, those with high rates of sexual partner change also appear to have a fairly high frequency of sex acts per unit of time. This observation is of great importance to a current debate on whether models of the spread of HIV should be based on rates of sexual partner change or on sexual acts per unit of time. Ideally, both distributed variables should be included, with an appropriate interaction term between the variables. In broad terms, however, the pattern recorded in Fig. 12 helps explain why, in studies of the probability of transmission of HIV, the rate of sexual partner change appears to be the most significant sexual behaviour variable in explaining the likelihood that an individual has acquired infection (Anderson *et al.* 1989a; May & Anderson 1988). Those with high rates of sexual partner change appear, on average, to have a high number of sexual acts per unit of time.

More generally, applying a statistical method widely used in ecology (Taylor’s power law; Taylor 1961) a plot of the relationship between the variance ( $\sigma^2$ ) in the number of different sexual partners per unit of time versus the mean number of partners ( $m$ ), on

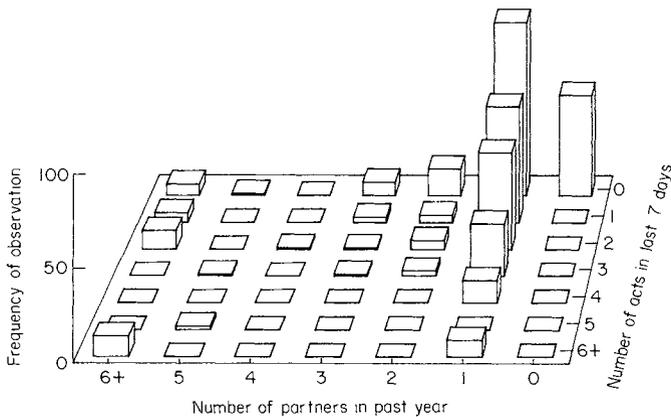


FIG. 12. Joint frequency distribution of the number of different sexual partners over the past year and the number of sex acts over the past 7 days (survey as defined in the text and legend to Fig. 11).

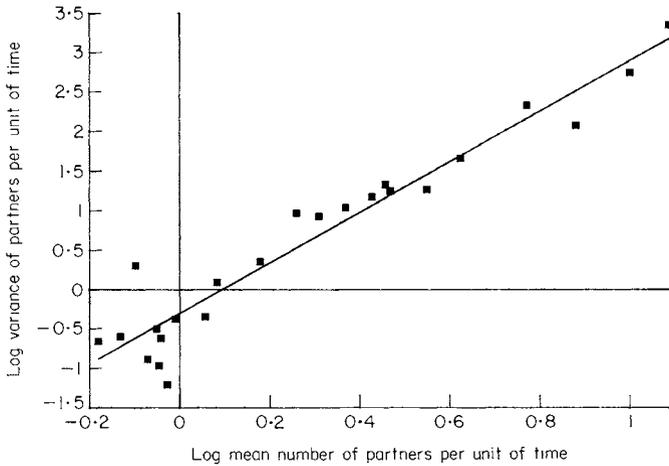


FIG. 13. Log-log plot of the variance ( $\sigma^2$ ) and mean ( $m$ ) of the distribution of the number of different sexual partners over past time intervals (1 month–lifetime) as recorded in a pilot survey of men and women in England and Wales in 1988–89 (see Johnson *et al.* (1989) for details of the survey). The squares record observed values and the line is the best fit linear model with slope approximately equal to 3. Means and variances were calculated for samples stratified by age, sex and period of recall (1 month–lifetime).

logarithm scales, produces a straight line. A power law exists between the variance and mean of the form  $\sigma^2 = am^b$ . Interestingly, unlike most other ecological applications of this method based on the considerations of organism abundance in space or time (see Taylor, Woiwood & Perry 1978), the recorded pattern for sexual behaviour reveals great variability where the power coefficient ( $b$ ) adopts a value of approximately 3 (in ecological applications the value of  $b$  is typically of the order of 2). For the pilot survey in England and Wales of sex partners per unit of time, the plot of variance ( $\sigma^2$ ) versus mean ( $m$ ) is recorded in Fig. 13. The different values represent different age and sex-classes and different time periods for recall of the number of different partners (1 month–lifetime). In a broader context, a compilation of quantitative data on rates of sexual partner change from surveys in homosexual and heterosexual communities, in developed and developing countries, reveals a similar pattern to that recorded for the England and Wales survey (Fig. 14). Despite the widely held view that human sexual behaviour is so variable in different societies that the search for pattern and process is likely to be unrewarding, the patterns displayed in Figs 13 and 14 reveal a useful empirical law (a power law), of the relationship between average behaviour and variability in behaviour, which is applicable to data from widely different societies of communities. Why the relationship is so consistent is unclear at present; it simply suggests that average behaviour in a given community sets the extremes in sexual behaviour (the frequency with which individuals have very high rates of sexual partner change) (Anderson & May 1988).

The importance of this observed heterogeneity to the spread and persistence of a sexually transmitted infection, such as HIV, is best illustrated by reference to the parameters that determine the magnitude of the basic reproductive rate of infection,  $R_0$  (the average number of secondary cases of infection generated by one primary case in a susceptible population). Simple models suggest that  $R_0$  can be defined as

$$R_0 = \beta cD \quad (6)$$

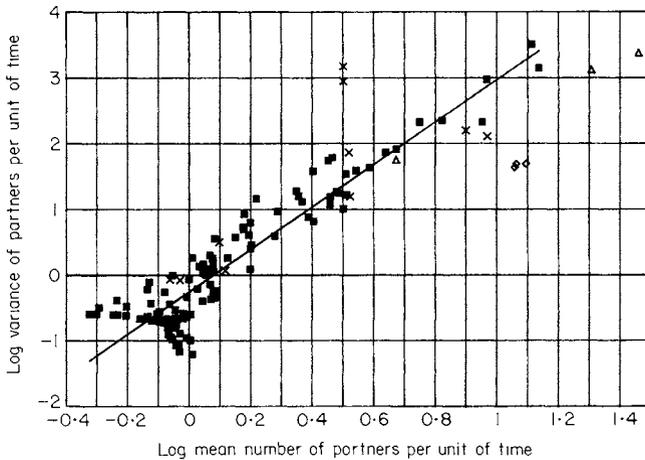


FIG. 14. Similar to Fig. 13 but recording data from a wide variety of published and unpublished surveys of sexual behaviour in heterosexual and homosexual communities in developed and developing countries (Anderson & May 1988). ■ data from heterosexual men and women in the general population of England and Wales; × data for heterosexuals attending sexually transmitted disease clinics in London; △ data from male homosexuals; ◇ data for heterosexual men in a Sub-Saharan African country.

where  $\beta$  defines the probability of transmission (per partner contact),  $c$  is the effective average rate of sexual partner change and  $D$  is the average duration of infectiousness of an infected person (Anderson *et al.* 1986; May & Anderson 1987). Assuming homogeneous mixing (= random) in the choice of sexual partners the effective average  $c$  is simply the mean number of different sexual partners per unit of time,  $m$ . With heterogeneous mixing, where few individuals have many partners and many have few (see Figs 10 and 11),  $c$  is approximately defined as

$$c = m + \sigma^2/m \quad (7)$$

where  $\sigma^2$  is the variance of partner change. Given the observed power law relationship between  $m$  and  $\sigma^2$ , eqn (7) can be written as

$$c = m + am^{(b-1)} \quad (8)$$

where  $a$  and  $b$  are the coefficients of Taylor's power relationship. Equations (7) or (8) suggest that, given the observed heterogeneity in rates of sexual partner change, the magnitude of the variance as opposed to the mean is likely to dominate the value of  $R_0$ . The major conclusion from this over-simplified example is that a small fraction of highly active individuals (the sexually active 'core') can maintain an infection within the general population despite the fact that average behaviour may be insufficient to maintain transmission. More generally, for an epidemic of HIV in a closed population (no recruitment or emigration) it can be shown that the fraction ever infected over the complete course of the epidemic is largely determined by the prevailing degree of heterogeneity in sexual activity. For example, Fig. 15 records this fraction as a function of the magnitude of  $R_0$  and the coefficient of variation (CV =  $\sigma/m$ ) of the number of different sexual partners per unit of time (May & Anderson 1987, 1988). Observed values of CV, calculated from reported partners of heterosexuals and homosexuals over past time

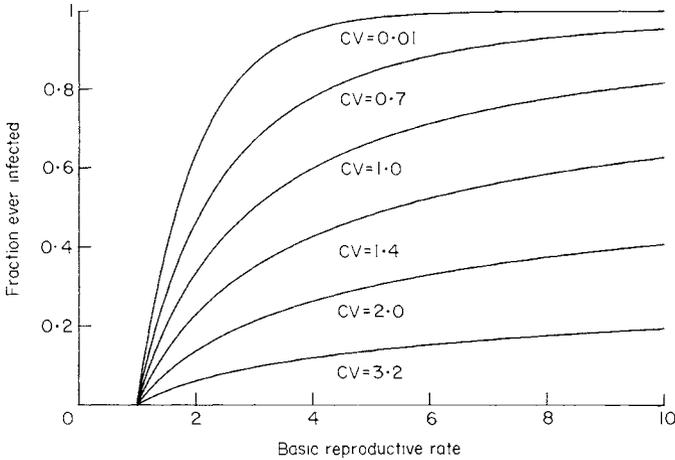


FIG. 15. The relationship between the fraction ever infected with HIV in an epidemic in a closed population and the coefficient of variation (CV) of the rate of acquisition of new sexual partners predicted by a simple model of the transmission dynamics of HIV (see May & Anderson 1988).

intervals of 1 year or more, lie in the range of 1.7 to greater than 2.0. From Fig. 15, this suggests that a low fraction (in the range of 20–30%) of the total population would acquire infection under these circumstances.

However, these calculations ignore a further source of heterogeneity which has a major impact on the pattern of the epidemic. Simple theory is usually based on the assumption of proportionate mixing in which an individual chooses partners at random according to their level of sexual activity (i.e. rate of sexual partner change). This assumption may not be correct since those in high sexual activity groups may choose individuals in their own group more or less frequently than you would expect by chance alone, by comparison with their choice of individuals from lower sexual activity groups. In other words, who mixes with whom, or the precise network of sexual contacts (stratified by sexual activity), is a major determinant of the spread of infection. In the terminology of population genetics or evolutionary biology we could describe restricted mixing within a class (i.e. like with like), where class is defined by the rate of sexual partner change per unit of time,

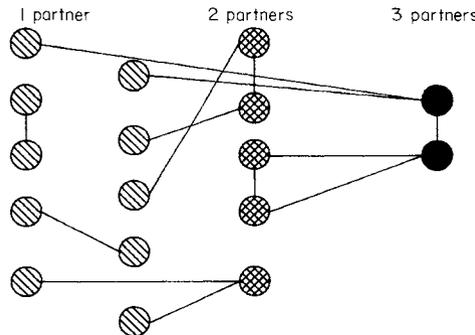


FIG. 16. A simple schematic illustration of a sexual partner choice network in which seventeen individuals are distributed into three sexual activity classes (one, two or three partners per unit of time) (see Anderson 1989).

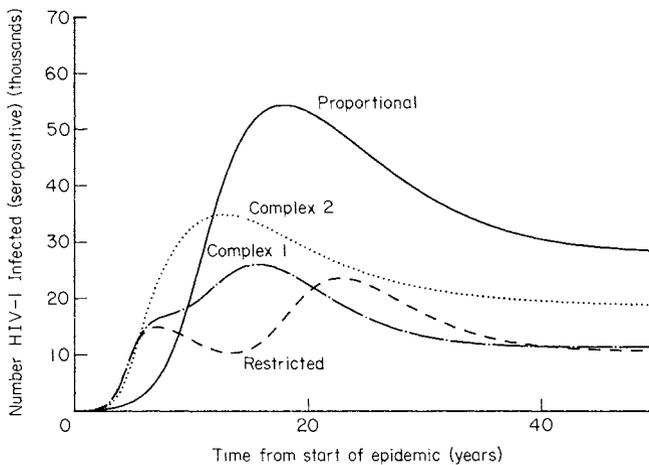


FIG. 17. Simulations of temporal trends in the number of people infected with HIV-1 in a male homosexual population (size at  $t=0$ , 500 000, 4% of the sexually active male population between the ages of 16 and 46 years in England and Wales). The model used to generate the trajectories is described in Gupta, Anderson & May (1989) and Anderson (1989) and incorporates distributed incubation and infectious phases, heterogeneity in sexual activity and recruitment of susceptibles. The different trajectories record predictions under different assumptions concerning the mixing or sexual partner choice matrix. Four simulations are recorded ranging from disassortative mixing (proportional) through two intermediary patterns (complex 1 and 2) to assortative mixing (restricted).

as assortative choice, and homogenous mixing across all classes as a type of disassortative choice (Gupta, Anderson & May 1989). A schematic illustration of a sexual partner choice network is presented in Fig. 16. Unfortunately, little data is available with which to decide whether sexual partner choice is highly assortative or disassortative. The reasons are obvious: it is one thing to ask in confidence how many different sexual partners an individual had contact with over a defined time interval, but it is quite another to follow this question up with a request for the names and addresses of the sexual partners in order to construct a network of contacts between individuals in a given community. However, what is clear from studies of mathematical models incorporating a mixing or network structure, is that the form of the 'who mixes with whom' function has a major impact on the predicted pattern of spread of HIV. An illustration is provided in Fig. 17 where numerical simulations of the HIV-1 epidemic in the male homosexual population in the U.K. (from the point of introduction of the infection at time  $t=0$ ) are recorded for different assumptions concerning the pattern of sexual partner choice. Restricted mixing represents an assortative pattern while proportional mixing represents a disassortative pattern (see Anderson 1989; Gupta, Anderson & May 1989; Jacquez *et al.* 1988). This area of research is an important one for future work and it has many parallels with work in ecology or evolutionary biology where, for example, spatial pattern or genetic heterogeneity, are determined by behavioural factors.

#### *Probability of fertilization*

A final example of the significance of heterogeneity in parasite distribution within its host population concerns its influence on the net fecundity of the parasite population. For

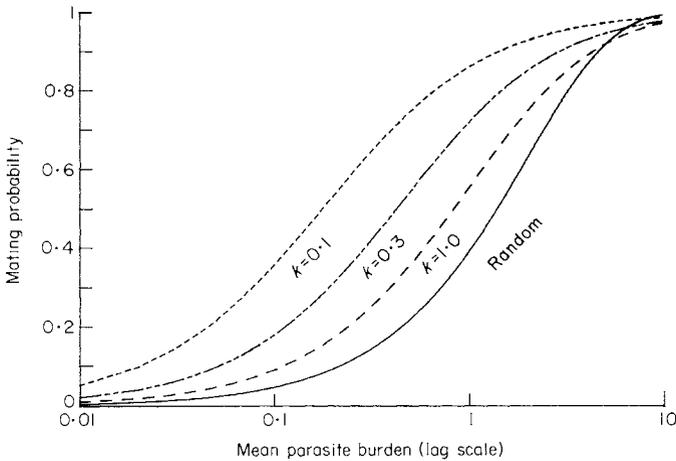


FIG. 18. The relationship between the probability that a female helminth parasite (polygamous, dioecious species) is mated (the mating probability) and the mean worm burden per host as a function of the degree of parasite aggregation within the host population, as measured inversely by the negative binomial parameter  $k$  (see May 1977; Anderson & May 1985).

dioecious species, such as nematode or digenean parasites, the occurrence of mating and fertilization within the isolated environment of the host dictates that the probability of finding a mate of the opposite sex, is dependent on the density of parasites within that host. This problem can be circumvented by hermaphrodites (many cestodes (tape-worms)), but even in these examples parasite density will determine the frequency of cross-fertilization between individuals. In population terms, the problem of finding a mate at low densities implies that net fecundity will depend on the distribution of parasite numbers per host. An illustration of this point is presented in Fig. 18 for a dioecious polygamous helminth, where the probability of a female worm being mated is plotted as a function of the mean parasite burden and the degree of aggregation of the parasite within the host population, as measured inversely by the negative binomial parameter  $k$  (May 1977; Anderson & May 1985b). As the degree of aggregation rises, the likelihood of a female worm being mated increases. In other words, these mating probability effects act as a kind of inverse density dependence on net parasite fecundity. This is counteracted at high parasite densities within individual hosts by the more familiar form of density dependence, where fecundity declines at high densities due to host immunological responses or competition for limited resources (Fig. 19). Again, the net severity of this latter type of density dependence is associated with the degree of parasite aggregation within the host population. The result of the interaction of these two countervailing forces, both functionally dependent on parasite density (one increases fecundity at high densities while the other decreases it), can generate multiple stable equilibria in mean parasite density (May 1977; Anderson 1980). The parallels with the population ecology of free-living species are many in this particular example, as heterogeneity in the parasite's distribution within its host population is directly analogous to spatial heterogeneity (or isolation) in the distribution of a free-living organism. In both cases the net severity of density-dependent constraints on population growth is intimately linked with the degree of heterogeneity in the distribution of abundance.

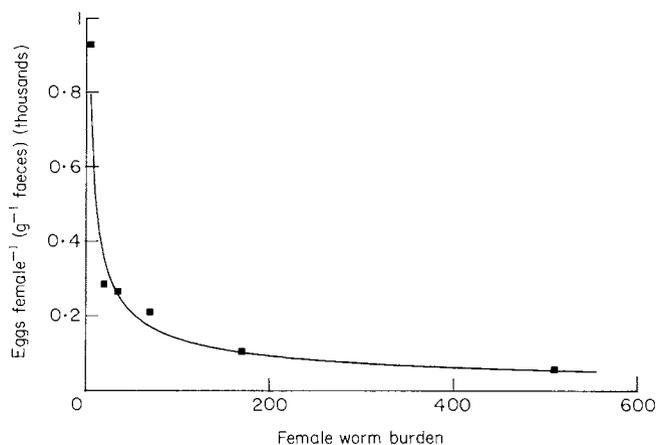


FIG. 19. Density-dependent fecundity in *Schistosoma mansoni* (Digenea) infections in humans (see Medley & Anderson 1985). Egg production ( $\text{g}^{-1}$  of faeces) is plotted as a function of female worm burden (■) and the best-fit power model is recorded by the solid line.

## CONTROL OF INFECTION AND DISEASE: ECOLOGICAL PERSPECTIVES

Much has been written in recent years concerning the basic ecological principles that underpin the design of programmes for the control of infectious disease spread in communities of hosts (Anderson & May 1985a, b; Nokes & Anderson 1988). The central problem in effective controls rests on the question of what proportion of the host population must be vaccinated, or treated with a chemotherapeutic agent, to block transmission. Subsidiary questions may concern the optimum age group to target for vaccination or treatment or, indeed, should control be targeted at particular individuals or groups in the population on the basis of sex, infection/disease status or other criteria.

The answers to these questions depend to a large extent on the transmission dynamics of the infectious agent in question and on its distribution and abundance within the host population. Life-cycle characteristics and the magnitude of the parasite's or infectious agent's basic reproductive rate,  $R_0$ , in the target host community have a major influence on the intensity and frequency of control intervention required to halt transmission. In the case of microparasitic organisms (viruses, bacteria and protozoa) the basic reproductive rate records the average number of secondary cases of infection generated by one primary case in a susceptible host population of defined density. The concept of  $R_0$  is directly analogous to Fisher's notion of the net reproductive potential of an organism; in the case of microparasites reproductive potential is defined as the generation of secondary cases of infection as opposed to the production of offspring who attain sexual maturity.

### *Vaccination and chemotherapy*

To block or interrupt transmission a sufficient proportion of the host population must be immunized, or treated with a drug that suppresses the likelihood of passing on the infection, such that the magnitude of  $R_0$  is reduced to less than unity ( $R_0 < 1$ ). More formally, it is possible to define the relationship between the control criteria (proportion of a birth cohort to be immunized,  $p$ , or proportion of the host population to be treated

with a drug,  $g$ ) and the magnitude of  $R_0$ . For example, in the case of vaccination against a viral or bacterial infection (where the vaccine gives life-long protection against infection) the criteria for a host population of constant size and age distribution is

$$\rho > [1 - 1/R_0]/[1 - V/L] \quad (9)$$

where  $V$  is the average age at which hosts are immunized and  $L$  is host life expectancy (Anderson & May 1985a). For certain types of infections the magnitude of  $R_0$  is related to the average age ( $A$ ) at which infection is acquired within the host population:

$$R_0 \sim L/A \quad (10)$$

where  $L$  is again host life expectancy. Hence, eqn (9) can be expressed only in terms of  $V$ ,  $A$  and  $L$ . It then becomes apparent that to block transmission the average age at immunization must be less than the average age at infection prior to the start of vaccination ( $V < A$ ). If this is not the case, mass vaccination will have little impact on transmission. The closer the value of  $V$  is to the average  $A$ , the higher the proportion of the population that must be immunized to block transmission (Fig. 20). Two general points emerge from this type of analysis. First, it is not necessary to immunize every host to block transmission: sufficient hosts must be immunized so that each primary case generates less than one secondary case. Second, the younger host are immunized, the easier it is to have a major impact on the net transmission of the infectious agent within the host population. Similar principles apply if we are using a drug to expel macroparasitic organisms (e.g. helminths) in hosts with persistent infections. In these cases  $R_0$  is defined for macroparasites in a manner similar to Fisher's definition for free-living organisms. It represents the average number of offspring produced by a female parasite that survive to join the reproductive age-classes within a host (Fisher 1930; Macdonald 1965; Anderson & May 1985a). For a chemotherapeutic agent of efficacy  $h$  (the proportion of the parasite burden killed by a single or short course of treatments) the proportion of the host

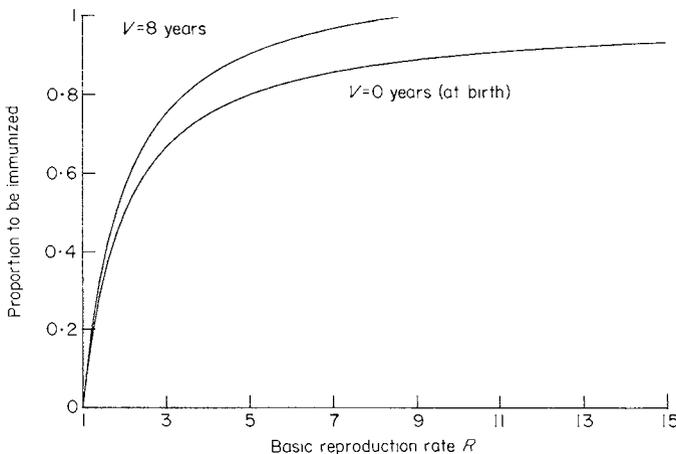


FIG. 20. The relationship between the proportion of the host population that must be immunized to block transmission and the reproductive potential of the infectious agent (as measured by the basic reproductive rate,  $R_0$ ) as predicted by eqn (9) for  $L = 70$  years and two values of the average age at vaccination  $V$ .

population that must be treated per unit of time (i.e. month<sup>-1</sup> or year<sup>-1</sup>) to block parasite transmission is given approximately by the relationship

$$g > \{1 - \exp[(1 - R_0)/Q]\}/h \quad (11)$$

where  $Q$  denotes the life expectancy of the mature worm in the human host (in units identical to  $g$ ) (Anderson 1982).

In practical terms, an immediate question that springs to mind is how can the magnitude of  $R_0$  be measured for a given infection in a defined host community? In the epidemiological literature, in contrast to that concerned with the ecology of infectious agents in non-human hosts, much use is made of immunological techniques to determine the presence or absence of antibodies specific to a particular infectious agent. For many viruses and some bacteria, the presence of antibodies reflects past infection (antibody production is often life-long following recovery from infection) and, as such, can be used to construct a profile of the proportion of hosts who have experienced infection by a given age (in epidemiological terms, a cross-sectional serological profile) (Fig. 21). Ignoring the decay of maternally derived antibody (a half-life of around 6 months in humans, for antibodies specific to viral antigens), the rapidity of the rise in the proportion who have experienced infection with age reflects the intensity of transmission and hence the magnitude of  $R_0$ . If the infection is not a major cause of mortality (disease-induced mortality complicates the interpretation of age-specific serology) and the per capita rate of infection is independent of age, then eqn (10) provides a means of calculating the magnitude of  $R_0$  given an age-stratified serological profile with which to estimate the average age at infection ( $A$ ) and the host's life expectancy ( $L$ ). These serological techniques are rarely used by ecologists for the study of the transmission dynamics of infectious diseases of mammals or birds, and yet they provide a good method for the estimation of transmission intensity.

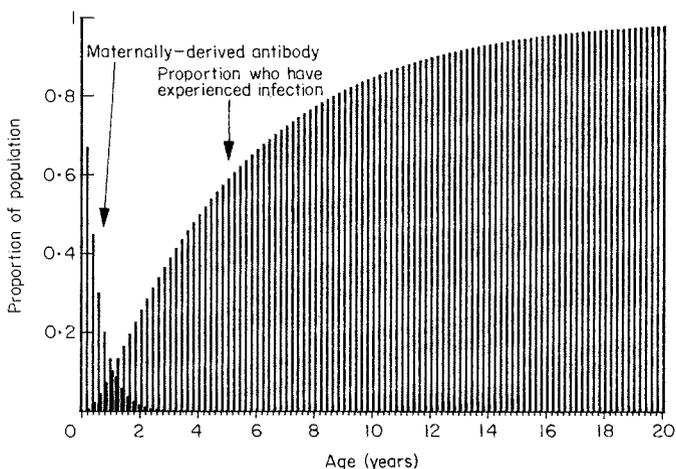


FIG. 21. A cross-sectional serological profile denoting changes with age in the proportion of a host population who have maternally derived protection against infection and who have experienced the infection. In generating the graph it was assumed that the rate of loss of maternally derived protection and the rate of acquisition of infection were constant and independent of age. The expected duration of maternal protection was set at 6 months and the average age at first infection was set at 5 years.

*Is control always beneficial?*

As noted in the Introduction, control programmes for infections of humans often act as a large-scale experiment in population perturbation within a two-species interaction (human–infectious agent). Tracking the abundance of the infectious agent following the introduction of control measures, allows various theories concerning the stability and population regulation of the two species interaction to be tested in a much more precise way than is normally possible in natural animal or plant communities.

The best examples of ‘natural’ perturbation experiments arise as a result of the instigation of mass vaccination in human communities. Theory predicts that a reduction in the net rate of transmission (a reduced reproductive rate of infection) of a directly transmitted virus or bacteria that induces lasting immunity following recovery from infection will result in an increase in the average age at infection and a lengthening of the inter-epidemic period between peaks in the incidence (case reports per unit of time) of infection (Anderson & May 1982). The lengthening of the inter-epidemic period is predicted to be less if transmission is age-dependent with most infection occurring in young children. The models from which these predictions are derived are based on coupled sets of partial differential equations representing changes in the densities of susceptibles, infecteds and immunes with respect to age and time (Anderson & May 1983, 1985a). These are easily adapted to mirror the known biological and epidemiological properties of many common childhood viral infections such as measles and rubella (German measles). In the Introduction, an example of the impact of mass vaccination on the incidence of measles in England and Wales was recorded and time-series analysis of this data set pre- and post-vaccination reveals a lengthening in the inter-epidemic period, from around 2 years prior to immunization to close to 3 years post-vaccination (Anderson, Grenfell & May 1984). One of the best examples of immunization increasing the average age at infection and inducing ripples in the age-stratified serological profile is provided by the history of rubella immunization in Finland. The programme adopted in Finland was as follows. From 1975 to 1982 immunization was targeted at girls only (to prevent congenital rubella syndrome (CRS) in babies born to mothers who contract rubella during the first trimester of pregnancy) in the age range of 12–18 years. Vaccination took place after the average age at infection (7–9 years prior to the start of immunization) and hence had little impact on the overall transmission of the virus. In November 1982, an additional programme of vaccination was introduced (using the triple measles, mumps and rubella vaccine, MMR) to cover young children in the age range 1–6 years. This new programme had an immediate effect on the net rate of transmission and it acted to shift the age distribution of cases upwards, increasing the average age of infection from 1983 onwards (Fig. 22). In addition, the major perturbation introduced by this sudden reduction in transmission induced a ripple in the age-stratified serological profile such that a cohort of susceptible children, just older than the age range covered by the vaccination introduced in 1982, is clearly discernible in the serological profiles for 1984 onwards (Fig. 23). The data displayed in Figs 22 and 23 is described in an excellent publication by Ukkonen & von Bonsdorff (1988). The ecological principle illustrated by this example is that highly non-linear patterns of population behaviour can be generated in two-species interactions following a perturbation from the endemic steady state. The predictions of simple models are well supported by the pattern observed in Finland.

An additional interest in this example concerns the question of whether what is good for the individual (i.e. vaccination) is always good for the community. If serious disease



FIG. 22. Occurrence of virologically proven rubella infection in different age groups, males and females combined, in Finland 1980–86 (from Ukkonen & von Bonsdorf (1988)) (see text for details).



FIG. 23. Occurrence of rubella IgG antibodies (evidence of past infection) in different age groups, males and females combined, in Finland 1980–86 (Ukkonen & von Bonsdorf (1988)) (see text for details).

more commonly occurs if infection is acquired at an older, as opposed to a younger, age then mass vaccination which increases the average age at infection can, in principle, act to increase the incidence of disease (as opposed to infection) (Anderson & May 1983; Knox 1980). The example of rubella is a good one as serious disease occurs in children (CRS) born to mothers who contract the infection in the first trimester of pregnancy. Hence, the age-specific risk of serious disease arising is directly equivalent to the age-specific fertility rate for women. To assess the likelihood that immunizing a fraction  $\rho$  of a cohort of children of age  $b$  is likely to increase the number of cases of infection in a defined age range (say the pregnancy age classes, 16–40 years; 99% of all births in most developed countries) it is possible to employ models to define a ratio of cases in that age range after

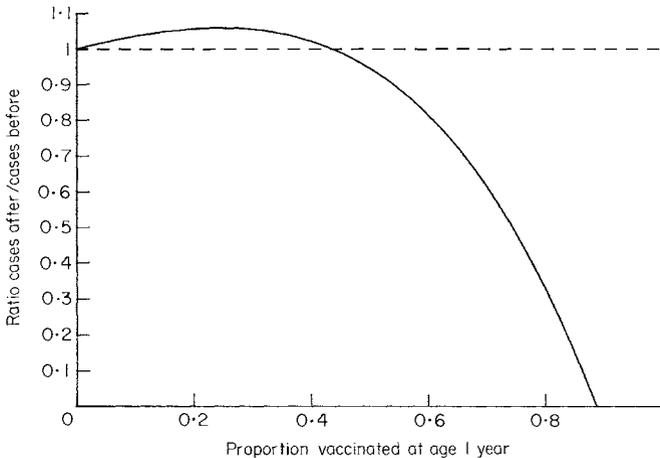


FIG. 24. Predicted impact of cohort immunization (at age 1 year) on the incidence of rubella infection (which can result in congenital rubella syndrome (CRS) in infants born to mothers who acquired infection in the first trimester of pregnancy), recorded as the ratio of the incidence of infection in women between 16 and 40 years old after immunization, divided by the incidence of infection in the same age-classes before the start of immunization (from Anderson & May 1983).

immunization divided by the number occurring in that age range before mass vaccination,  $q$ . An illustrative calculation of this ratio for rubella in England and Wales is presented in Fig. 24 under the assumption that the average age at infection was approximately 9 years before vaccination ( $A=9$  years,  $R_0=8.0$ ) and that immunization, at various levels of coverage (different values of  $\rho$ ) took place at 1 year of age (see Anderson & May 1983, Fig. 3). Note that for low levels of vaccination the number of cases of infection between the ages of 16–40 years rises over that pertaining prior to control. The moral is clear: vaccination programmes must aim to achieve high levels of coverage if the incidence of disease resulting from infection rises with age. The precise form of the ‘risk by age’ function matters in these calculations and hence attention must be given to its quantification (defined per case of infection) over all age-classes (Anderson & Grenfell 1986; Anderson, Crombie & Grenfell 1987).

A very topical example of this issue at present concerns the use of chemotherapy for those infected with the human immunodeficiency virus type 1 (HIV-1). At present the only drug of proven efficacy in the treatment of AIDS patients is zidovudine (AZT), although the degree to which it prolongs life is unclear. Recently a trial of the use of AZT in asymptomatic patients (those infected with HIV but who have not as yet developed AIDS) in the U.S.A. was halted because AZT appeared to delay the onset of symptoms of disease (Cherfas 1989). Currently, of those untreated, approximately 50% have developed AIDS 10 years after infection with the virus (Fig. 25). The question under debate in many developed countries is whether or not to licence the use of AZT for asymptomatic as well as AIDS patients.

Whether this is sensible or not depends on two factors. Most obvious is the need for the drug to have proven benefit for infected persons. However, even if it is of benefit to the individual it may not be of benefit in a community-wide context, if treated persons remain infectious to others and continue to have unprotected sex with susceptible partners. On the basis of the data available from drug trials it is not possible to say at present, with any

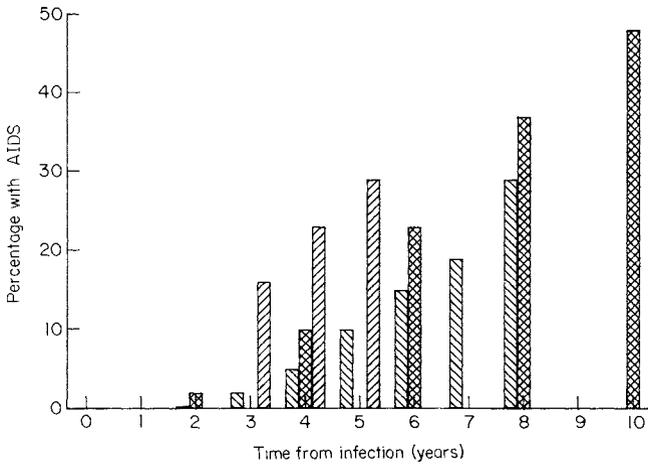


FIG. 25. Percentage of patients with AIDS as a function of time since infection with HIV-1 based on cohort studies in different at-risk groups: ▨ transfusion patients (Sweden); ▩ haemophiliacs (U.S.A.); ▤ homosexual men (U.S.A.) (from Bacchetti & Moss 1989).

certainty, what the impact of the drug is on infectivity. An optimistic view would be that as AZT appears to reduce detectable levels of the virus, it is also likely to reduce infectiousness. However, this remains to be substantiated. Similar concerns would apply to treatments termed ‘immunotherapy’, where immunization acts to booster the immune system and delay the onset of disease, but is unable to eliminate the virus from the body of the patient.

To consider the community aspects of such treatments it is necessary to examine the population ecology of viral spread and persistence in human communities. For the purpose of illustration, consider a very simple model of the transmission dynamics of HIV (for more complex and more realistic treatments of this problem, see Anderson *et al.* 1989a; May & Anderson 1987, 1988; Anderson *et al.* 1986; Jacquez *et al.* 1988) within a male homosexual community divided into susceptibles ( $X$ ), infecteds who are not vaccinated and not on drug treatment ( $Y$ ), vaccinated susceptibles ( $V_x$ ) and infecteds who are vaccinated and are on drug treatment ( $V_y$ ). The model is formulated in general terms to account for cohort immunization (= immunotherapy) where a proportion  $\rho$  of new recruits to the sexually active classes receive immunotherapy, immunotherapy applied to susceptibles at a constant per capita rate ( $s$ ) and the treatment of infecteds at a per capita rate ( $r$ ). The four equations for  $X$ ,  $Y$ ,  $V_x$  and  $V_y$  are

$$dX/dt = \mu N_0(1 - \rho) - (c\lambda + \mu + s)X \tag{12}$$

$$dY/dt = c\lambda X - (v + \mu + r)Y \tag{13}$$

$$dV_x/dt = \mu N_0\rho - (c\lambda + \mu)V_x + sX \tag{14}$$

$$dV_y/dt = c\lambda V_x + rY - (\mu + d)V_y \tag{15}$$

The term  $\mu N_0$  defines the net rate of recruitment of susceptibles to the sexually active age classes,  $1/\mu$  defines the average duration of sexual activity,  $c$  defines the mean rate of sexual partner change  $1/(v + \mu)$  is the infectious period of untreated infecteds and  $1/(d + \mu)$  is the infectious period of treated and vaccinated infecteds. The term  $\lambda$  defines the per

partner rate of infection. The most pessimistic assumption is that treated or vaccinated people (the class  $V_y$ ) have the same infectiousness as untreated or unvaccinated persons. In this situation the force of infection is defined as

$$\lambda = \beta(Y + V_y)/N \quad (16)$$

where  $N$  is the total population size of infected and uninfected persons and  $\beta$  is the per partnership probability of transmission. Those leaving the infectious classes are assumed to develop AIDS and die. The optimistic assumption (with respect to the individuals infected) is that treatment or vaccination prolongs the period between infection and the development of AIDS (i.e.  $1/(v + \mu) < 1/(d + \mu)$ ). Note that in eqn (14) it is assumed that vaccination prolongs the time period for the development of disease but does not protect against infection.

A simple method of assessing the community level impact of treatment with AZT or immunotherapy is to consider the equilibrium population size. Its magnitude is a reflection of the mortality induced by AIDS. In the absence of infection the equilibrium population size  $N^*$  is simply  $N^* = N_0$ . A measure of the impact of treatment or immunotherapy is provided by the ratio of the equilibrium population size in the presence of infection and treatment or immunization,  $N_T$ , divided by the equilibrium population size in the absence of treatment/immunization but in the presence of infection  $N_A$  (i.e.  $N_T/N_A$ ). If treatment or immunization is beneficial at the community level (as opposed to the level of the individual) the ratio will be greater than unity in value; if it is not, the ratio will be less than unity in value. For the model defined in eqns (12)–(16),  $N_T$  is given by (see Anderson, May & Gupta 1990) ( $s = 0$ ,  $r = 0$ ,  $\rho \neq 0$ )

$$N_T = [(1 - \Psi)N_0]/[1 - (1/\beta c)(\Psi/\phi)] \quad (17)$$

where 
$$\phi = [\rho/(\mu + d)] + [(1 - \rho)/(\mu + v)] \quad (18)$$

and 
$$\Psi = [(d\rho)/(\mu + d)] + [v(1 - \rho)/(\mu + v)] \quad (19)$$

Consider the case where only treatment with AZT occurs, plus some cohort vaccinations ( $\rho \neq 0$ ,  $s = 0$ ,  $r \neq 0$ ), then  $N_T$  is given by

$$N_T = [(1 - \Psi_T)N_0]/[1 - (1/\beta c)(\Psi_T/\phi_T)] \quad (20)$$

where

$$\theta = \rho + [(1 - \rho)r/(r + \mu + v)] \quad (21)$$

$$\theta_T = [\theta/(\mu + d)] + [(1 - \rho)/(r + \mu + v)] \quad (22)$$

and

$$\Psi_T = [(d\theta)/(\mu + d)] + [(1 - \rho)v/(r + \mu + v)] \quad (23)$$

In both cases  $N_A$  is given by  $N_A = \mu N_0/[(\mu + v)(1 - v/\beta c)]$ .

A plot of the ratio  $N_T/N_A$  is presented in Fig. 26 as a function of the proportion of susceptible recruits protected by immunotherapy,  $\rho$ , and the ratio of the infectious period in untreated/vaccinated people divided by the infectious period in treated/vaccinated people ( $(\mu + d)/(\mu + v)$ ). If the ratio is less than unity in value treatment/immunotherapy is of benefit to the individual patient (prolongs the period before AIDS develops). Note that in Fig. 26 the ratio  $N_T/N_A$  falls below unity in value for certain values of  $\rho$  (low values) and the ratio of the duration of infectiousness (low to medium values). The area below unity is increased if the product  $\beta c$  (probability of transmission times the rate of sexual partner

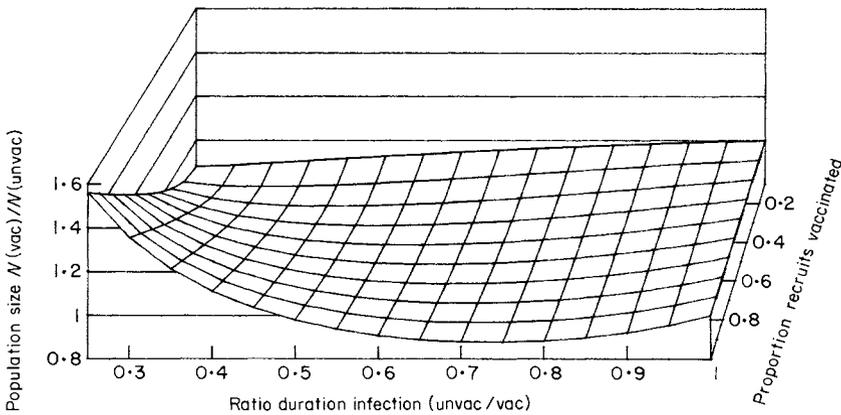


FIG. 26. A plot of  $N_T^*/N_A^*$  (see eqns (17) and (20) in the text) as a function of the proportion of recruits to the sexually active age-classes immunized, and the ratio of the duration of infection (= infectiousness) in unvaccinated persons divided by the duration in vaccinated individuals (see text). The duration of infection in unvaccinated person was set at 8 years ( $\beta c = 0.2 \text{ year}^{-1}$ ,  $r = 0$ ,  $s = 0$ ).

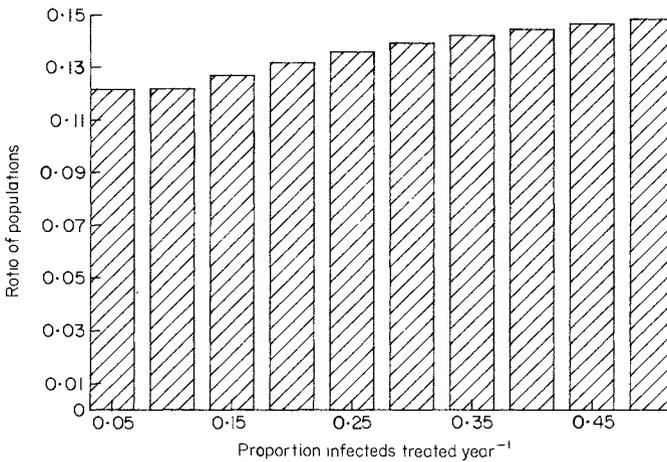


FIG. 27. The ratio  $N_T^*/N_T^*$  (see eqns (17) and (20) in the text) as a function of the proportion of infecteds treated with AZT per year (see text). The duration of infection (= infectious) in treated individuals is assumed to be extended from 8 years in untreated persons to 32 years in treated individuals ( $\beta c = 0.2$ ,  $p = 0$ ,  $s = 0$ ).

change) is low and may be zero if  $\beta c$  is large. Similar problems arise if we consider a population that is just receiving AZT treatment ( $r \neq 0$ ,  $\rho = 0$ ,  $s = 0$ ) as illustrated in Fig. 27. In this example, a rather extreme case is considered where continual treatment extends the infectious period by a factor of 4 (from 8 years to 32 years) and does not decrease the infectiousness of treated individuals. The rate of treatment,  $r$ , is represented as a proportion treated per year,  $q$ , where

$$q = [1 - \exp(-r)] \tag{24}$$

The model defined above is far too simple to represent the true complexity of HIV

transmission and hence the patterns presented in Figs 26 and 27 must be interpreted with caution. Complexities that must be added include heterogeneity in sexual activity (both in rates of partner change and who mixes with whom) and transmission between different at-risk groups (i.e. intravenous drug users, homosexuals and heterosexuals). In addition, pessimistic assumptions were made in the analyses, e.g. treated infected persons were assumed not to decrease their levels of sexual activity by comparison with uninfected persons, and infectiousness was assumed to be the same in treated and untreated persons. However, the simple model serves as a starting point for more refined calculations and, more importantly, highlights the need to measure how drug treatment or immunotherapy influences attributes of significance to transmission such as infectiousness. It is often falsely assumed that what is good for the individual is always good for the community. The two examples discussed in this section, rubella and AIDS, suggest that this is not always the case.

#### *Population genetics and population dynamics*

Melding theories in the fields of population genetics and population dynamics presents a formidable task because the resulting models, with their frequency and density-dependent effects (that represent changes in gene frequencies and population abundances), tend to be highly non-linear and very complex in structure. Population ecologists tend to consider changes in abundance without reference to changes in genetic composition of the population, while population geneticists tend to examine changes in gene frequencies without reference to changes in population abundance.

The rapid advances taking place in molecular, biochemical and immunological fields are beginning to provide a series of tools, e.g. DNA fingerprinting and the polymerase chain reaction (PCR), which are potentially of great use to the ecologist wishing to examine the genetic structure of a particular population. Specifically, in the area of infectious disease research on viruses and bacteria, the PCR method raises the hope that it will be possible to reliably detect, and perhaps even quantify, the presence of different genetic strains of a microparasite from samples of hosts drawn from natural populations. These new methods therefore add impetus to the collection of data and to the development of theories that meld genetic and population dynamic elements.

A start has been made in this direction, specifically in the area of infectious disease agents of humans (May & Anderson 1983; Beck 1984; Forsyth *et al.* 1988; Anderson, May & Gupta 1989). In the field of ecology, one of the earliest papers on the theory of frequency and density-dependent selection in epidemics of disease was that by Gillespie (1975). This followed a much earlier suggestion by Haldane (1949) that infectious agents were probably very important in the maintenance of genetic variability within host populations, and perhaps even played a role in the evolution and maintenance of sexual reproduction. This particular topic has spawned much interest in recent years (Hamilton 1980; Hamilton & Zuk 1982); however, at present the field is strong on hypotheses but weak on factual information.

In the area of parasite control, genetic factors play a major role, as drugs or vaccines impose strong selective pressures on pathogen population. In the field of vaccine development, genetic diversity within infectious agent populations presents many problems in the design of a useful product (e.g. influenza viruses, HIV and the malarial parasites). Recently, some progress has been made in the development of a theoretical framework, incorporating genetic and ecological factors, to examine how genetic heterogeneity can influence the design and application of disease control programmes.

One such example is a model of the transmission of helminth parasites which are subject to selective pressures imposed by either drug treatment in the host population, or the host's immunological defences. The same model is appropriate for both situations, because the immune system and chemotherapy act within an individual host to select the most resistant strains of the parasite (Anderson, May & Gupta 1989).

The models tend to be very complex even with a simple genetical system of a single locus and two alleles representing resistant ( $r$ ) and susceptible ( $s$ ) genes, given the necessity with macroparasites to keep track of the distribution of parasite numbers per host and to represent sexual reproduction in dioecious polygamous species by a mating function that takes account of the distribution of female and male worms in the host population (see May 1977; Anderson 1980; Anderson, May & Gupta 1989). Complex models can generate complex patterns of change in gene frequencies and parasite abundance, such as widely fluctuating frequencies within a parasite population of constant size. In the context of control, the consequences of a particular programme of drug application may not be immediately obvious without the support of model projections.

An interesting example of the difficulties inherent in prediction is provided by helminth parasites in vertebrate hosts. For many species of importance as aetiological agents of disease in humans and domestic animals, effective chemotherapeutic agents are available. However, where drug treatment is applied intensively and repeatedly in populations, evidence of the evolution of drug-resistant parasite strains usually emerges. This is particularly apparent in the treatment of intestinal nematodes of cattle and sheep (Pritchard *et al.* 1980). In a simple model of this problem based on the assumption of a

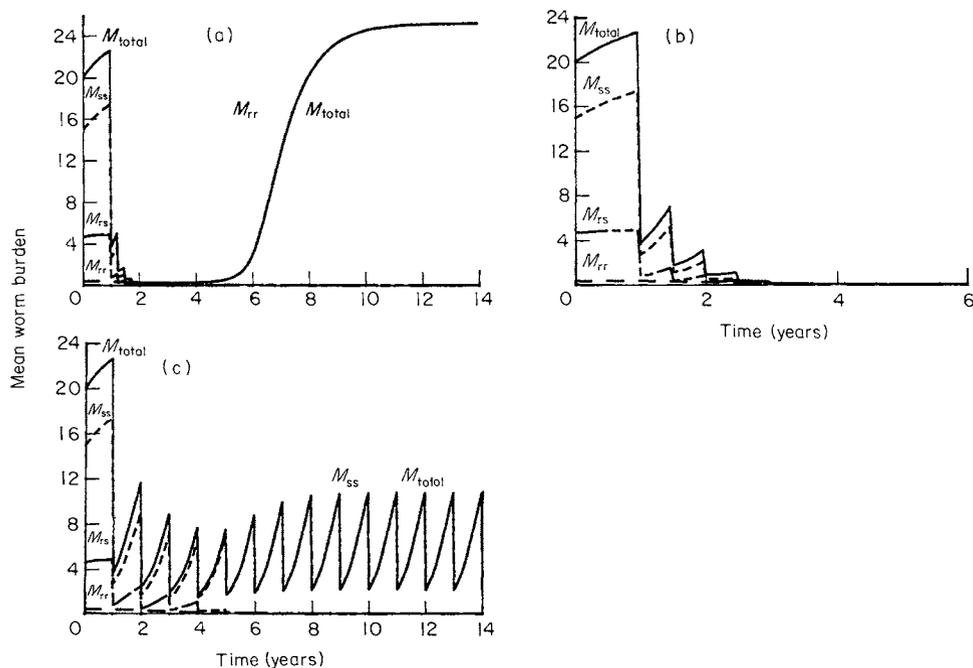


FIG. 28. Simulated trajectories of changes in mean worm burden of three different genotypes (homozygote susceptible,  $M_{ss}$ , heterozygote,  $M_{rs}$ , and homozygote resistant,  $M_{rr}$ ) in a host population subject to chemotherapeutic treatment at (a) 3-monthly intervals, (b) 6 monthly intervals, and (c) yearly intervals (see text and Anderson, May & Gupta 1989).  $M_{total}$  records the total worm burden ( $= M_{rs} + M_{ss} + M_{rr}$ ).

single locus and two alleles (resistant and susceptible), which incorporates diploid genetics, details of sexual reproduction, parasite distribution and density-dependent constraints on parasite transmission, Anderson, May & Gupta (1989) found threshold effects, relating to the intensity and frequency of drug treatment, which defined whether or not the parasite was controlled, or whether the resistant strain prevented effective control. An example is presented in Fig. 28 which records simulated temporal trajectories of the mean parasite burden,  $M$ , in a population of hosts (parasites are assumed to be distributed in a negative binomial manner with clumping parameter  $k = 0.57$ ; parameters were set to mimic *Ascaris lumbricoides* in humans) stratified by genotype (homozygous resistant,  $rr$ , homozygous susceptible,  $ss$  and heterozygous,  $rs$ , where  $M_{\text{total}} = M_{rs} + M_{rr} + M_{ss}$ ). In Fig. 28, treatment occurred at (a) 3-monthly, (b) 6-monthly, and (c) yearly intervals. When treatment is very frequent (Fig. 28a), the resistant allele is fixed and the mean parasite burden attains its precontrol level, with the population consisting entirely of the homozygous resistant genotype. At intermediate frequencies of treatment (Fig. 28b), the parasite population is eradicated, while at infrequent treatment intervals (Fig. 28c) the mean worm burden is suppressed and the homozygous resistant genotype is eradicated, such that the suppressed population consists entirely of homozygous susceptible and heterozygous genotypes. The elimination of the susceptible allele in Fig. 28a is a result of the inverse density-dependent effects created by the mating probability term for dioecious macroparasites discussed in the second section (see Fig. 18). The moral is clear from this example: the intensity and frequency of treatment must be finely tuned to avoid negating the usefulness of the chemotherapeutic agent. This very brief discussion of genetic and ecological interactions, as applied to the study of parasite control, glosses over much detail. The general point illustrated by this example is the need for much greater attention in future research on population dynamics, on the subtle interplay between genetic and ecological factors.

### Biological control

Much interest currently centres on the search for alternatives to pesticides for the control of plant or invertebrate pest species, to reduce pollution of the natural environment. Some interest has centred on the use of viruses, bacteria and protozoa as agents in the control of insect pest species (Tinsley 1979). Baculoviruses, in particular, appear to have great promise for the control of certain insect species, such as forest lepidopteran pests.

Ecological study of the population dynamics of insect pathogens can help to identify the main characteristics required of a pathogen to control a given pest species, and suggest how the pathogen can be used to the greatest effect in depressing host abundance. These questions have been the subject of some attention recently, particularly with respect to the development of simple mathematical models of two-species interaction (Anderson & May 1981; Anderson 1982; Hochberg, Hassell & May 1990). Theory can provide a very useful framework for considering the merits of different approaches in the use of pathogens as biological control agents. One approach is to select a pathogen for a once-only introduction into the target pest population, on the basis of the choice of the ideal biological properties to maximize suppression of host abundance. Another approach is to use the pathogen in a manner similar to a chemical pesticide, such that it is repeatedly introduced into the population when pest abundance is high. A simple framework to help examine these issues is provided by a mathematical model that describes temporal changes in the densities of susceptible ( $X$ ) and infected ( $Y$ ) hosts plus the density of free-

living infective stages ( $W$ ) of the pathogen (virus particles, bacterial spores or protozoan cysts). As described in Anderson & May (1981) an appropriate microparasite model is

$$dX/dt = a(X + Y) - bX - vWX + \gamma Y \quad (25)$$

$$dY/dt = vWX - (\alpha + b + \gamma)Y \quad (26)$$

$$dW/dt = \lambda Y - (\mu + vH)W \quad (27)$$

Here  $a$  is the per capita birth rate of the host,  $b$  is the per capita death rate,  $v$  is the transmission coefficient,  $\gamma$  is the rate of recovery from infection (note no immunity),  $\alpha$  is the disease-induced host mortality rate,  $\lambda$  is the rate of production of infective stages per infected host, and  $\mu$  is the mortality rate of the infective stages. In the absence of infection the host population grows exponentially at a per capita rate  $r = a - b$ .

The dynamics of this simple system (which ignores complications such as vertical transmission, spatial factors and pathogen effects on host fecundity) is fairly complex. The pathogen may or may not regulate host abundance to a stable or oscillatory equilibrium depending on the values of the parameters. If an equilibrium occurs, total host population size  $H^*$  ( $H^* = X^* + Y^*$ ) is given by

$$H^* = [\alpha/(\alpha - r)]H_T \quad (28)$$

where

$$H_T = [\mu/(v\lambda)]\{(\alpha + b + \gamma)/[1 - (\alpha + b + \gamma)/\lambda]\} \quad (29)$$

This rather complex expression shows that a subtle interplay between the biological parameters of the association determines the degree to which the pathogen is able to depress host abundance. Of major importance, however, is high pathogenicity ( $\alpha$ ) relative to the host's intrinsic growth rate ( $r$ ), a high rate of production of infective stages ( $\lambda$ ), high transmission efficiency ( $v$ ), long-lived infective stages ( $\mu$  small), and a low rate of recovery from infection ( $\gamma$ ).

With respect to repeated introductions, at a rate  $A$  per unit of time, eqn (27) must be modified to

$$dW/dt = A + \lambda Y - (\mu + vH)W \quad (30)$$

It can be shown that a critical rate of introduction exists,  $A_c$ , above which the pathogen eradicates the host species (Anderson & May 1981), where

$$A > A_c = \lambda Y_0 = [\mu r(\alpha + b + \gamma)]/[v(\alpha - r)] \quad (31)$$

where  $Y_0$  is the equilibrium density of infected hosts in the absence of repeated introductions of the pathogen ( $A = 0$ ).

Analytical and numerical studies of simple models like that outlined above can greatly facilitate the interpretation of observed patterns of disease in natural populations and the impact of different control strategies. An illustration of this point is provided in Fig. 29 which records a numerical study of the model defined by eqns (25)–(30) designed to mirror the interaction between a lepidopteran forest pest and a nuclear-polyhedrosis virus. The insect is assumed to have a net reproductive rate ( $r$ ) of 1 year<sup>-1</sup> and the virus is assumed to produce a long-lived infective stage ( $1/\mu = 1$  year) and to be of high pathogenicity ( $\alpha = 5$  year<sup>-1</sup>). The pathogen regulates host population growth creating stable cycles in host and pathogen abundance with an inter-epidemic period of  $c. 10$  years. At year 50 in the simulation, repeated introduction of viral infective stages is initiated ( $A = 500$  year<sup>-1</sup>) and control damps the oscillatory fluctuation to a stable equilibrium. A number of points are of interest in this example. First, the virus which induces high mortality in the host, is able

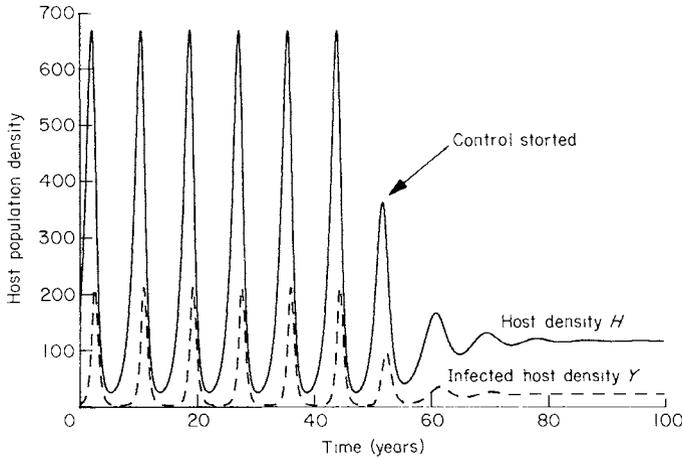


FIG. 29. Numerical solutions of eqns (25)–(27) and eqn (28) in the main text. Control was introduced at year 50. Parameter values  $a=2$ ,  $b=1$ ,  $v=0.001$ ,  $\alpha=5$ ,  $\gamma=50$ ,  $\mu=1.0$ ,  $A=0$  for  $t < 50$  and  $A=500$  for  $t > 50$  ( $\text{year}^{-1}$ ) (see Anderson & May 1981).

to generate long-term oscillatory fluctuations in host abundance. Second, peak abundance of infected hosts occurs after peak abundance in the total host population. This pattern could tempt an observer to conclude, falsely, that the pathogen was not responsible for inducing the cycles. Third, and finally, perturbations induced by the introduction of control measures can damp an oscillatory interaction to a stable state. This latter observation could, in principle, be used to test ideas concerning the dynamical interaction between host and pathogen via field trials using the pathogen as a biological control agent for insect–virus interactions which are oscillatory in character in natural or managed habitats.

More broadly, there is a natural tendency amongst field ecologists to underestimate the value of theory in guiding the interpretation of observed pattern, on the grounds that too many simplifying assumptions are made in model construction despite known biological complexity. A counter argument is that simple models, as illustrated above, can induce complex patterns of dynamical behaviour. It is therefore important to be aware of this when constructing hypothesis to interpret observed changes in species abundance.

### PERSISTENCE OF GENETICALLY MODIFIED ORGANISMS IN NATURAL HABITATS

The likelihood that a genetically altered organism will persist in a natural or managed habitat into which it is released, is a question of some practical significance at present, given current discussions concerning the safety of planned releases of genetically modified or engineered organisms. Certain genetic engineering techniques involve modified bacteria, where plasmids are used as vehicles for the transference of genetic material. Potential applications include the use of engineered bacteria to remove or detoxify pollutants in terrestrial or aquatic habitats, or to enhance the growth and productivity of crop plants (e.g. nitrogen-fixing bacteria). In assessing safety matters, or the regulation of such releases, a major question centres on the likely stability or persistence of the introduced genetic material.

This issue is difficult to assess in any precise manner, given our limited understanding of the role plasmids play in the transference of genetic material in natural populations of bacteria (Levin 1981). Much past research in this area has centred on the role plasmids play in the transference of drug resistance in bacterial populations that can be pathogenic to man or domestic animals.

The population-based theory of the transmission of infectious disease agents can help to sharpen discussion in this area, an approach pioneered by Levin and co-workers (Levin & Lenski 1985). By way of a simple illustration we consider the spread and persistence of a plasmid, containing the 'engineered' genetic information, in a bacterial population. Specifically, we address the question of whether or not the plasmid can persist, given that it confers a selective disadvantage on the bacteria, by comparison with a plasmid-free organism (= host).

For simplicity, we employ a simple population model to represent changes in the densities of plasmid-free bacteria,  $X(t)$ , and genetically modified bacteria carrying the plasmid,  $Y(t)$ , with respect to time  $t$ . For generality, we assume that the genetic information can be transmitted between bacteria by the plasmid via (i) asexual reproduction (binary fission) in a manner akin to vertical transmission, (ii) sexual reproduction (conjugation) in a manner akin to horizontal transmission, and (iii) via the lysis of carrier bacteria and the release of plasmids as infectious particles ( $W(t)$ ) capable of infecting susceptible bacteria. We further assume that the plasmid-carrying bacteria ( $Y$ ) is at a selective disadvantage, such that its per capita death rate exceeds that of a plasmid-free host by an amount  $\alpha$ . During binary fission a fraction  $f$  of 'new births' are assumed to inherit the plasmid from the infected parent. The model is as follows:

$$dX/df = aX + ap(1-f)Y - bX - \beta XW - \gamma XY \quad (32)$$

$$dY/df = apfY + \beta XW + \gamma XY - (\alpha + b)Y \quad (33)$$

$$dW/df = \lambda(\alpha + b)Y - dW - \beta XW \quad (34)$$

Here  $a$  denotes the per capita birth rate (via asexual reproduction),  $b$  is the per capita death rate,  $\alpha$  is the extra death rate arising from carrying the plasmid,  $p$  is the factor by which the plasmid reduces the per capita rate of reproduction of its host,  $\lambda$  is the average number of free plasmids released by the death of an infected bacterium,  $d$  is the death rate of free plasmid particles,  $\gamma$  is the transmission coefficient which denotes the likelihood that an uninfected host will acquire the plasmid during conjugation with an infected bacterium, and  $\beta$  is the transmission coefficient for infection following contact between a free plasmid and an uninfected host. Note that in the absence of infection by the plasmid the bacterial population grows exponentially at a rate  $r$ , where  $r = a - b$ .

The properties of this simple model are straightforward. The plasmid-bearing bacterial population will persist, despite the selective disadvantage conferred by carrying the plasmid, provided the case reproductive rate of the infected bacterium,  $R_0$ , is equal to, or exceeds, unity in value. For the model represented by eqns (32)–(34), the value of  $R_0$  represents the average number of secondary cases of infection generated by one plasmid-carrying bacterium in a population of  $X$  plasmid-free bacteria. It is defined as follows

$$R_0 = [apf + [\beta\lambda(\alpha + b)X/(d + \beta X)] + \gamma X]/(\alpha + b) \quad (35)$$

Here the terms  $apf$ ,  $\beta\lambda(\alpha + b)X/(d + \beta X)$  and  $\gamma X$  denote the respective contributions made to transmission by asexual reproduction (= vertical transmission), lysis and the release of free plasmid particles and conjugation (= horizontal transmission), while  $1/(\alpha + b)$  denotes the life expectancy of a plasmid-bearing bacterium.

As a consequence of the extra mortality arising from carrying the plasmid, the growth of the total bacterial population ( $X + Y$ ) may be regulated to a stable equilibrium by the plasmid provided the following constraint is satisfied

$$\alpha > (apf - b). \quad (36)$$

In the simpler case where plasmid-bearing bacteria are unable to reproduce (a very severe selective disadvantage), regulation always occurs. If eqn (36) is not satisfied, the total population grows exponentially with the plasmid maintained within it, provided  $R_0 > 1$ . In other words, independent of regulation, the persistence of the plasmid-bearing population depends on the magnitude of  $R_0$ .

When regulation occurs, the proportion of the population that are plasmid-bearing,  $y$ , is simply

$$y = r/\alpha \quad (37)$$

Thus, if the selective disadvantage conferred by carrying the plasmid is small ( $\alpha \rightarrow r$ ) a very high fraction will be infected, and vice versa.

If the plasmid is only able to transmit between bacteria by the vertical route of binary fission ( $\beta = \gamma = 0$ ), it will be unable to regulate population size and, more importantly, unable to persist if it confers a selective disadvantage ( $\alpha > 0$ ,  $0 < p < 1$ ). A component of horizontal transmission via conjugation, or host lysis and the release of plasmids that are able to infect other bacteria (perhaps a bacteriophage that induces host-cell destruction but carries the plasmid's genetic code) is therefore essential if the genetic information borne by the plasmid is to persist.

In summary, this very simple example of the introduction and persistence of genetic information via the release of a bacterial plasmid highlights a few points of general importance in any assessment of the safety or wisdom of such releases. First, the mathematical framework commonly employed in the study of the transmission dynamics of infectious agents (i.e. microparasites) can be adapted to mirror the spread of genetic material via plasmids, bacteriophages or transposons. Second, whether or not the material will persist or spread in its host population (or other hosts, given that some plasmids can transfer material between bacterial species) depends on the values of the population parameters that determine the magnitude of the case reproductive rate of the plasmid (or genetic information). Given that many parameters are involved, even in the simplest of models (see eqn (35)), it may be necessary to find experimental or observational methods to directly measure (or estimate) the value of  $R_0$  in defined conditions. Third, and finally, a component of horizontal transmission is essential for the persistence of the genetic information contained in the plasmid.

## POPULATION ECOLOGY OF THE IMMUNE SYSTEM

Plant and animal species live in a very hostile world filled with a bewildering, and ever-changing, array of infectious disease agents. To combat this continued and varied assault, both plants and animals have developed (via evolution) various defence mechanisms. These include the production of chemicals by plants to discourage or inhibit herbivore and infectious agent attack, and the sophisticated immunological defence systems of vertebrate hosts. In the latter case, these defences can create acquired immunity to a specific infectious agent.

Recent advances in immunology and molecular biology are enabling researchers to

classify, more and more finely, the various types of cells and factors (i.e. enzymes, antibodies, etc.) produced or released by cells that constitute the immune system of vertebrates. It is becoming increasingly apparent that such systems are very complex in structure containing many cell types and factors, whose responses (i.e. rate of cell division, rate of production of a given factor) are non-linearly related to the densities of each other and the invading infectious agent against which they are directed. An exciting field of research, which is currently in its infancy, and to which population ecologists can make an important contribution, is the study of the dynamical interactions within the immune system and how these influence the population growth and decay of an infectious agent within an individual host. Broadly speaking, we could refer to this area of study as the population ecology of the interaction between the immune system and invading infectious agents.

In this section, we consider two problems to illustrate how analyses of the population ecology of an immunological response to any infectious agent can help to interpret observed patterns, both in the course of infection within an individual host, and in the distribution of infection and disease within a population or community of hosts. As in preceding sections, simple mathematical models are employed to sharpen discussion and interpretation, and to help identify what needs to be measured in order to improve our understanding of observed pattern.

#### *Human immunodeficiency virus type 1 (HIV-1)*

The current pandemic of the Acquired Immunodeficiency Syndrome (AIDS) throughout most countries in the world has resulted in an intensive international research programme to discover ways of preventing infection with the aetiological agent, HIV-1, and of slowing the progression from infection to the disease AIDS. At present no vaccines are available and only a single drug, zidovudine (AZT), is thought to slow the progression from infection to disease. Current estimates of the time from infection to the diagnosis of the disease AIDS (the incubation period of AIDS) are around 10 years for sexually active adults. Once AIDS develops, life expectancy is between 1 and 2 years.

The virus induces disease via its cytopathic effects on one of the key cells in the human immune system, the helper-inducer T-lymphocytes. The virus binds to, and infects, the lymphocyte via the T4 (CD4) surface receptor molecule. Cell infection and subsequent cell death results in a drastic and often almost complete destruction of the helper T-cell population (a fall in the T4 cell count in peripheral blood). The consequence is a much impaired cell-mediated immune response, which makes the human host highly susceptible to a range of opportunistic infections that are normally non-pathogenic in the uninfected host. The peripheral T4 cell count in infected patients declines slowly over the 10-year incubation period of the disease. A diagrammatic illustration of the processes involved in cell infection and destruction is presented in Fig. 30.

The interaction between the T4 cell and HIV-1 presents a fascinating problem in population ecology. The interaction is complex and subtle. It constitutes on the one hand a host-parasite interaction between T4 cell and virus and, on the other hand, a predator-prey interaction between cell and virus. In the latter context, the T4 cell plays a major role in initiating and controlling the immunological defences of the human host which are targeted to destroy free virus in the body and cells infected with the virus. The dynamic interplay between the host-parasite interaction and the predator-prey interaction, arising solely from the association between two 'species' (the T4 cell and HIV-1), is likely to

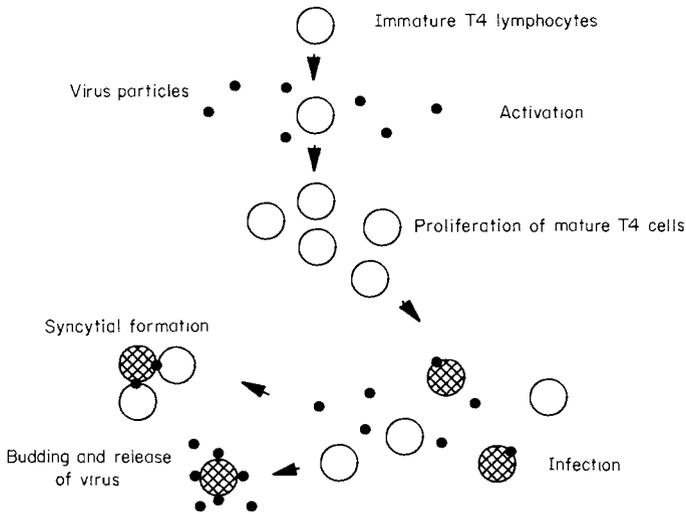


FIG. 30. Schematic diagram of the interaction of the human immunodeficiency virus type 1 (HIV-1) with T4 lymphocytes in the human host.

induce highly non-linear patterns of population growth and decay. To dissect these we consider a very simple model of the major processes involved in the interaction.

We define the densities of immature T4 cells, mature uninfected T4 cells, mature infected T4 cells and free virus in the blood as  $M(t)$ ,  $X(t)$ ,  $Y(t)$  and  $V(t)$ , respectively, at time  $t$ . Immature T4 cells are recruited into the blood system from the thymus at a constant rate  $\Lambda$  and die at a constant per capita rate  $\mu$ . On contact with free virus at a net rate  $\gamma MV$  these cells mature and begin to proliferate at a per capita rate  $a$  and die at a per capita rate  $\mu$  ( $r = a - \mu$ ). Infection results from contact between uninfected mature cells and free virus at a net rate  $\beta XV$ , and infected cells die at a per capita rate  $\alpha$  ( $\alpha \gg \mu$ ). Infected cells release virus via budding and cell death at a net rate  $\lambda \alpha Y$ , and free virus either dies at a net rate  $dV$  or is absorbed by uninfected mature cells at the net rate  $\beta XV$ . We mirror the action of the uninfected mature T4 cells in initiating the immunological attack on free virus ( $V$ ) and infected cells ( $Y$ ) by net mortality rates on infected cells and free virus, in proportion to the density of uninfected cells  $X$ , of  $hVX$  and  $gXY$ , respectively. These assumptions give four coupled differential equations for  $M(t)$ ,  $X(t)$ ,  $Y(t)$  and  $V(t)$  as follows:

$$dM/dt = \Lambda - \mu M - \gamma MV \quad (38)$$

$$dX/dt = \gamma MV + rX - \beta XV \quad (39)$$

$$dY/dt = \beta XV - \alpha Y - gXY \quad (40)$$

$$dV/dt = \lambda \alpha Y - dV - hVX - \beta XV \quad (41)$$

As the death rate ( $d$ ) of free virus is much greater than that of infected and uninfected cells ( $d \gg \alpha > \mu$ , the life expectancy of free virus ( $1/d$ ) is thought to be a matter of minutes or hours by comparison with life expectancies of a few days to many days, respectively, for infected and uninfected cells), we 'collapse' the system of four equations to three by substituting the equilibrium value for  $V$ , derived from eqn (41), into eqns (38)–(40). The

set of assumptions embodied in eqns (38)–(41) are a very simple mirror of the known complexity of the interaction and they ignore much detail. Two examples of processes ignored in the model are the role of infected cells in stimulating the maturation of immature T4 cells, and contact between infected and uninfected cells that results in the formation of giant cell syncytia and the subsequent death of both types of cell.

As discussed in Anderson & May (1989) and Anderson (1989), this very simple model exhibits a wide range of possible dynamical behaviours. For the virus to be able to establish within the host, the basic reproductive rate of the virus (now defined for within-host dynamics as the average number of secondary infections of T4 cells induced by one infected cell when introduced into a population of size  $X$  of uninfected cells),  $R_0$ , must exceed or equal unity in value. From eqn (40) it can be seen that

$$R_0 = (\beta\lambda\alpha X) / [(d + hX)(\alpha + gX)] \quad (42)$$

Note that the virus-induced infected cell death rate,  $\alpha$ , appears in both the denominator and numerator of the expression for  $R_0$ . Thus, interestingly, the reproductive potential of the virus increases as  $\alpha$  rises in magnitude to approach an asymptotic value (Fig. 31). This suggests that during the course of infection, evolution within the virus population may favour strains with increased pathogenicity to the T4 host cell. There is some evidence from clinical studies of infected patients that viral strains isolated late in the course of infection are more cytopathic than those isolated early on in the incubation period (Fenyo, Albert & Asgo 1989). If the basic reproductive rate of an infected cell is less than unity in value ( $R_0 < 1$ ) the virus is unable to establish within the host. In such circumstances,  $V$  and  $Y$  tend to zero, the population of immature inactivated T4 cells settles to the equilibrium  $X^* = \Lambda/\mu$  and the population of activated cells increases indefinitely ( $X \rightarrow \infty$ ) owing to clonal expansion. The action of suppressor cell activity can be represented by subtracting a term  $cX^2$  from the right-hand side of eqn (39), such that the activated cells will obtain an equilibrium at a high population density given by  $X^* = r/c$ . Whether or not suppressor cell activity is included in the model, the individual patient (= host) will possess antibodies to the virus (i.e. HIV-1 seropositive), but will be uninfected provided  $R_0 < 1$ .

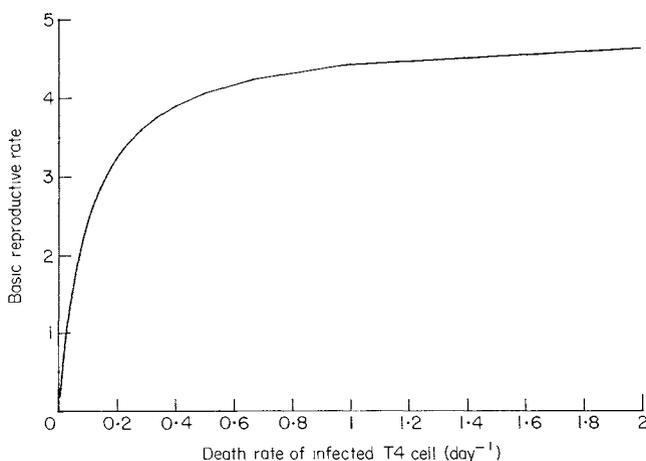


FIG. 31. Relationship between the basic reproductive rate of HIV-1,  $R_0$ , (generation of infected T4 cells) and the pathogenicity of the virus to its host cell ( $\alpha \text{ day}^{-1}$ ) (see eqn (42) in the main text).

If  $R_0 > 1$  the virus can establish and two qualitatively different possibilities may arise. These are best identified by making the simplifying assumption that the immune system has a negligible effect on infected cells by comparison with the mortality induced by infection ( $\alpha \gg gX$ ). If  $R_0 > 1$  and

$$(\lambda - 1) > h/\beta \quad (43)$$

the virus establishes and regulates the density of activated cells ( $X + Y$ ) to a stable or oscillatory equilibrium (oscillations are more likely to arise when  $(\lambda - 1)$  and  $h/\beta$  are comparable in magnitude). The biological interpretation of eqn (43) is that the rate of production of virus by infected cells must exceed the ratio of the coefficient of virus killing by uninfected activated cells ( $h$ ) divided by the coefficient of activated cell infection by the virus ( $\beta$ ). When eqn (43) is satisfied the system exhibits an initial burst of high viraemia, and then settles to, or oscillates around, a state where the abundance of activated T4 cells is regulated by the virus. Interestingly, in this regulated state, the proportion of infected cells may be very low (much less than 0.1%) provided the death rate of infected cells is high ( $\alpha$  large). Thus, severe depression of lymphocyte abundance (below the 'resting' state of inactivated cells,  $X^* = \lambda/\mu$ ) is not inconsistent with the observation that only a very small fraction of T4 cells harbour the virus in an infected patient (Schnittman *et al.* 1989) (Fig. 32). The equilibrium prevalence of infected cells,  $y^*$  ( $= Y^*/(X^* + Y^*)$ ) is approximately given by

$$y^* \sim 1/(1 + \alpha/r) \quad (44)$$

If the inequality defined by eqn (43) is not satisfied, but  $R_0 > 1$ , the virus can establish but its effects are not sufficient to halt the proliferative growth of the activated T4 cell population (the  $rX$  term outruns the  $\beta XV$  term in eqn (39)). If we added the realistic refinement of suppressor cell activity to the right-hand side of eqn (39), the system settles to, or oscillates around, a state with relatively high abundance of activated cells, both infected and uninfected. In summary, this simple model exhibits three possible patterns of dynamical behaviour: one where virus is eliminated: one without virus and activated T4 cells regulating each other; and one with the virus present but with suppressor cell activity primarily responsible for regulating activated cell abundance.

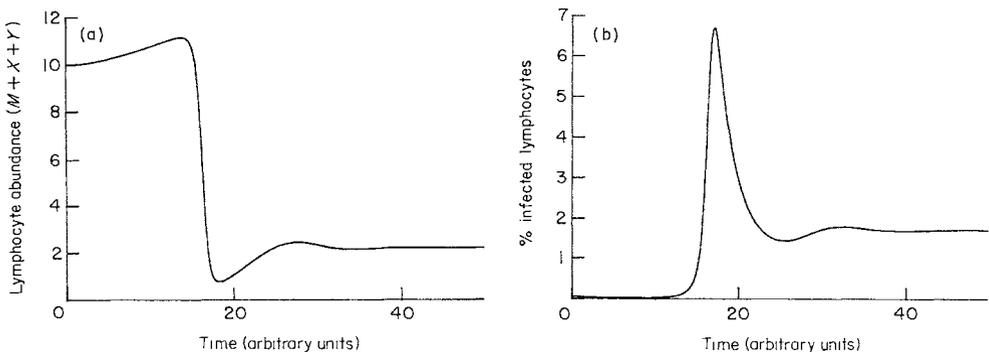


FIG. 32. Numerical solutions of eqns (38)–(41) in the main text with parameter values  $\Lambda = 1.0$ ,  $\mu = 0.1$ ,  $\gamma = 0.01$ ,  $r = 0.1$ ,  $\beta = 0.001$ ,  $\alpha = 2.0$ ,  $g = 0.01$ ,  $\lambda = 5.0$ ,  $d = 0.5$ ,  $h = 0.01$  (arbitrary time units); (a) changes in lymphocyte abundance; (b) changes in the percentage of cells infected with HIV-1.

The virus was introduced into the host at time  $t = 0$ .

We now consider the state in which virus and T4 cells are strongly interacting (via the concomitant host–parasite and predator–prey interaction) to regulate each others' abundance, and examine what happens when a second infection is introduced: the so-called opportunistic infection (viral, bacterial, fungal or protozoan). Prior to its arrival, T4 cell abundance is depressed via the cytopathic activities of HIV, although only a small percentage of cells are infected. It is assumed that the so-called opportunistic infection stimulates these same T4 cells to proliferate by clonal expansion. The dynamical behaviour produced by the introduction can be complicated, resulting in apparently chaotic fluctuations in HIV abundance, amongst other possible forms of behaviour. The population size of the opportunistic infection is represented by  $I(t)$  and the action of this population is described by adding an extra stimulation or proliferation term to the right-hand side of eqn (39) of the form  $kXI$ :

$$dX/dt = \gamma MV + rX + kXI - \beta XV \quad (45)$$

We also require an equation for  $I(t)$ :

$$dI/dt = \hat{a}I - sIX \quad (46)$$

Here  $\hat{a}$  denotes the per capita growth rate of the opportunistic infection and the term  $sIX$  represents the killing of the infectious agent by antibody or cell-mediated action (whose severity of action is proportional to the density of uninfected activated T4 cells). Equations (38), (45), (40), (41) and (46) represent the new expanded model, describing concomitantly the dynamics of HIV and the opportunistic infection. We start by considering the dynamics of the system in the absence of HIV. After an initial bout of pathogen growth which stimulates proliferation of the lymphocytes, the activated cells always eliminate the opportunistic infection.

When HIV is present the arrival of the opportunistic infection can result either in oscillatory fluctuations (which can have large magnitudes) in the abundance of HIV and the opportunistic infectious agent, or in chaotic dynamical behaviour. What happens is that HIV prevents the elimination of the new infection and the two together, via

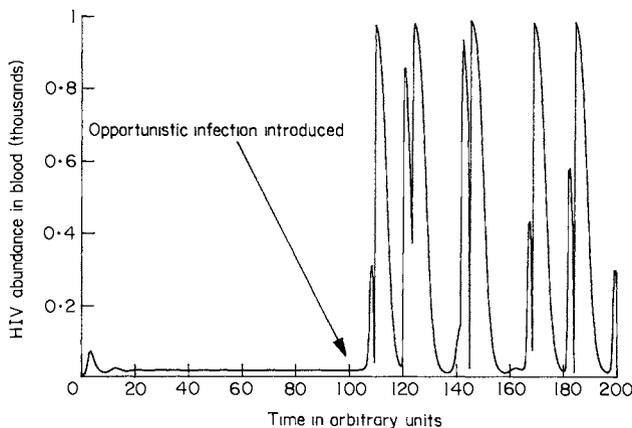


FIG. 33. Numerical solutions of eqns (38)–(41) and eqns (45)–(46) in the main text. HIV-1 was introduced at time  $t=0$ , and the opportunistic infection ( $I$ ) was introduced at time  $t=100$  (see Anderson & May 1989). The graph records predicted changes in HIV abundance ( $V$ ) in the blood stream.

interaction with the immune system, can trigger erratic and high amplitude fluctuations in HIV abundance (Fig. 33). A simple method of displaying simulated time trajectories of fluctuations in HIV and lymphocyte abundance is to plot the two variables in a phase space with free virus ( $V(t)$ ) plotted on the vertical axis and the concentration of activated uninfected lymphocytes ( $X(t)$  reflects the activity of the immune system, such as the production of antibodies directed against the virus) plotted on the horizontal axis. In Fig. 34 two such plots are recorded, with values taken at weekly time intervals over the first 100 time units of simulation (weeks) following infection with HIV (Fig. 34a) and over the second 100 time units following the acquisition of the opportunistic infection (Fig. 34b). For comparison, data from two groups of patients in hospitals in London (R. Tedder & A. Smith, personal communication) are recorded in Fig. 35, where one group are patients who had recently become infected and the second group are patients who were showing symptoms of disease (AIDS-related complex or AIDS). The plots are of HIV antigenaemia (assumed to reflect concentration of virus in the blood) and a measure of the

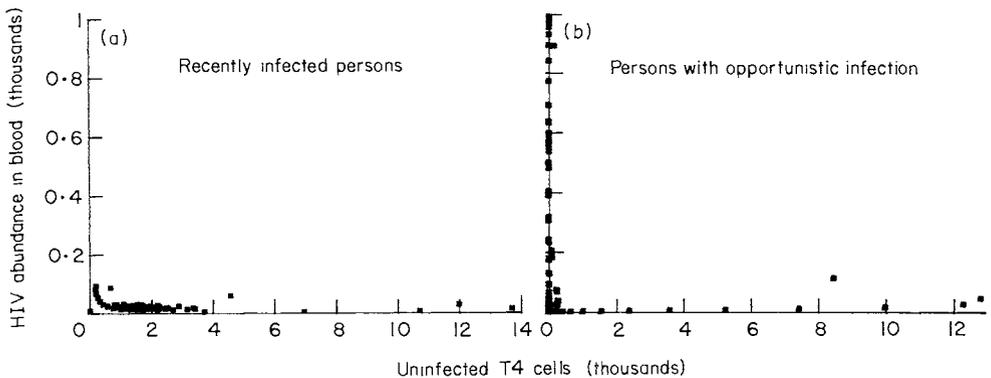


FIG. 34. Predicted relationship between HIV abundance in the blood ( $V$ ) and uninfected T4 cell abundance ( $X$ ) (eqns (38)–(41) plus eqns (45)–(46)). The points represent values of  $V$  and  $X$  at different instances in time. The relationship is recorded (a) in the absence of the opportunistic infection but in the presence of HIV, and (b) when both HIV and the opportunistic infection are present.

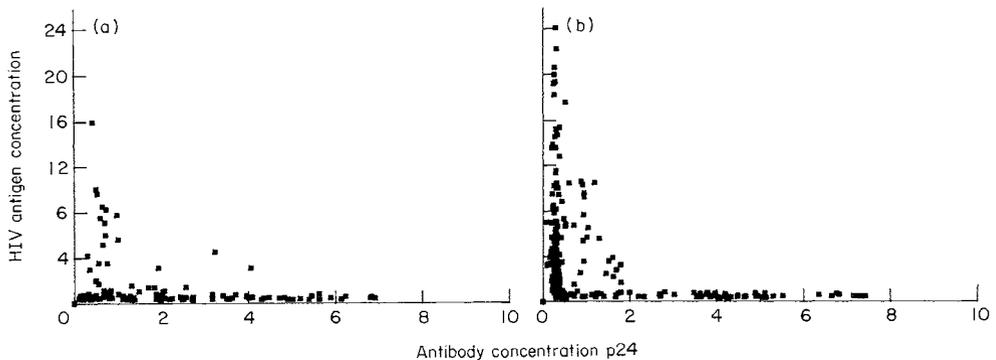


FIG. 35. Observed relationships between HIV-1 antigenaemia (p24 antigen) and antibody concentration (p24 antibodies) in (a) patients recently infected, and (b) patients with ARC (AIDS-related complex) or AIDS (data from R. S. Tedder and A. Smith).

immunological response of the patient (as measured by p24 antibody titres). Note how the patterns generated by the model crudely mirror those observed in the two sets of patients.

The model outlined above is obviously a gross oversimplification of the known complexity of the interaction of HIV with the human immune system. However, even this very simple mirror generates very complex patterns of dynamical behaviour and, in qualitative terms, captures a number of observed features. These are: (i) a very slow decline in T4 cell abundance following infection; (ii) a very low percentage of infected cells concomitant with severe depression of lymphocyte abundance; (iii) a long period between infection and the development of disease; (iv) the collapse of the immune system when HIV and the opportunistic infection are present together and (v) 'phase-plane' relationships between virus abundance and immunological activity similar to those observed.

Three general points emerge from this example. First, simple biological hypothesis can generate complicated patterns of non-linear behaviour. Second, an improved understanding of the progression from infection to disease will, in part, depend on a better appreciation of the population ecology of the immune system and its interaction with HIV. Third, and finally, the model is a very crude mirror of known biological detail and hence it serves purely as a starting point towards constructing more detailed and realistic models as our factual knowledge increases. Of the many refinements that must be taken into account, perhaps the most important is the emergence of different genetic strains of the virus via mutation and selection by the immune system during the long period from infection to the development of the disease AIDS. Interestingly, the simple model outlined above suggests that selection within an individual patient to maximize the net reproductive rate of the virus may result in the evolution of more cytopathic strains during the course of infection.

#### *Parasitic infection and immunosuppression*

Infectious agents have evolved many ways of evading immunological attack to enhance both their population growth and persistence within an individual host, and transmission between hosts. These mechanisms include antigenic variation within the host (i.e. the trypanosome parasites), location within immunological privileged sites, such as parts of the central nervous system (i.e. the herpes viruses) or within the immune system itself (i.e. HIV and the *Leishmania* protozoan parasites), and evasion of immunological attack via immunosuppression where the parasite directly or indirectly intervenes to block or suppress the development of an effective immunological response. The latter mechanisms are more commonly associated with infection by complex multicellular parasites such as helminths. They are thought to be responsible, in part, for the observation that many helminth infections are persistent in character within a host, despite evidence of specific immunological responses directed against the parasite.

In trying to dissect and understand why some infections manage to persist while others are rapidly eliminated by the host, the population ecology of the interaction between the parasite and the immune system is an obvious area for investigation. In this second example of the relevance of ecological research to an understanding of infection and immunity we focus on helminth infections of humans, such as the directly transmitted intestinal nematodes (e.g. *Ascaris lumbricoides*), and consider the question of parasite persistence and host immunosuppression.

In order to focus the discussion, we consider a simple model of the accumulation of infection by an individual host and the interaction between the immune system

represented, as in the previous case of HIV, by immature T4 cells,  $M(t)$ , plus activated mature T4 cells,  $X(t)$  and parasite abundance,  $P(t)$ . As before, immature cells ( $M$ ) are recruited from the thymus at a rate  $\Lambda$ , die at a per capita rate  $\mu$  and are activated to mature at a net rate  $\gamma MP$ . Activated mature cells ( $X$ ) proliferate at a rate  $r$ , are suppressed at a net rate  $cX^2$  and are deactivated by factors released by the parasite (perhaps a factor to block the action of interleukins which stimulate proliferation) at a net rate  $\beta XP$ . Parasites accumulate in the host as a result of immigration (= infection) at a constant rate  $A$ , die at a per capita rate  $d$  and are killed by the activated T4 cells at a net rate  $sXP$ . These assumptions give the following coupled differential equations for  $M$ ,  $X$  and  $P$ :

$$dM/dt = \Lambda - \mu M - \gamma MP \quad (47)$$

$$dX/dt = \gamma MP + rX - cX^2 - \beta XP \quad (48)$$

$$dP/dt = A - dP - sXP \quad (49)$$

The novelty in the formulation of this problem hinges on the specific recognition that the parasite is able to release a factor, or factors, that deactivate T4 cells that were specifically stimulated to mount an immunological attack against the parasite's antigens (the term  $\beta XP$  in eqn (48)). Note that in the absence of an immunological response the parasite population would increase monotonically to a stable equilibrium  $P^* = A/d$ . Similarly, in the absence of the parasite the immature unstimulated T4 cells would settle to a stable equilibrium  $M^* = \Lambda/\mu$ .

The dynamical properties of this model are most easily examined by the use of phase planes. We consider the association between the density of activated cells ( $X$ ) and the burden of parasites ( $P$ ) by plotting the equilibrium relationship between the two as defined by the following relationships which are derived from eqns (47)–(49) by setting the derivatives equal to zero:

$$X = [- (\beta P - r) + [(\beta P - r)^2 + 4c\gamma P\Lambda/(\mu + \gamma P)]^{1/2}] / 2c \quad (50)$$

$$X = (A - dP) / sP \quad (51)$$

These functions are plotted for a range of values of  $P$  in Figs 36 and 37 for defined values of the parameters. The first point to note is that multiple stable equilibria exist for given sets of parameter values. Two stable points (highlighted by dashed circles in Figs 36 and 37) are separated by an unstable equilibria. When alternate stable states exist they represent either high parasite burden and low immunity, or low parasite burden and high immunity. As illustrated in Fig. 36, exposure to infection (perhaps early in a child's life), as denoted by the magnitude of the parameter  $A$ , defines whether a person moves to the state of high immunity or low immunity. Paradoxically, low exposure results in high immunity and high exposure generates low immunity. This is a direct consequence of the immunosuppressive effects of the parasite. Interestingly, if worm burdens are cleared by chemotherapy, on subsequent re-exposure to infection those with low immunity (as a consequence of high exposure to infection in early life) are likely to return to the high worm burden state, and vice versa. The model suggests that experiences of infection early in life are likely to predispose individuals to low or high worm burdens. This conclusion is supported by epidemiological observations in human communities with endemic infection. An example is presented in Fig. 37 in which worm loads of *Ascaris lumbricoides* are recorded for 177 people in a rural setting in India before drug treatment (which expels the worms) and following a 12-month period of reinfection (Haswell-Elkins, Elkins &

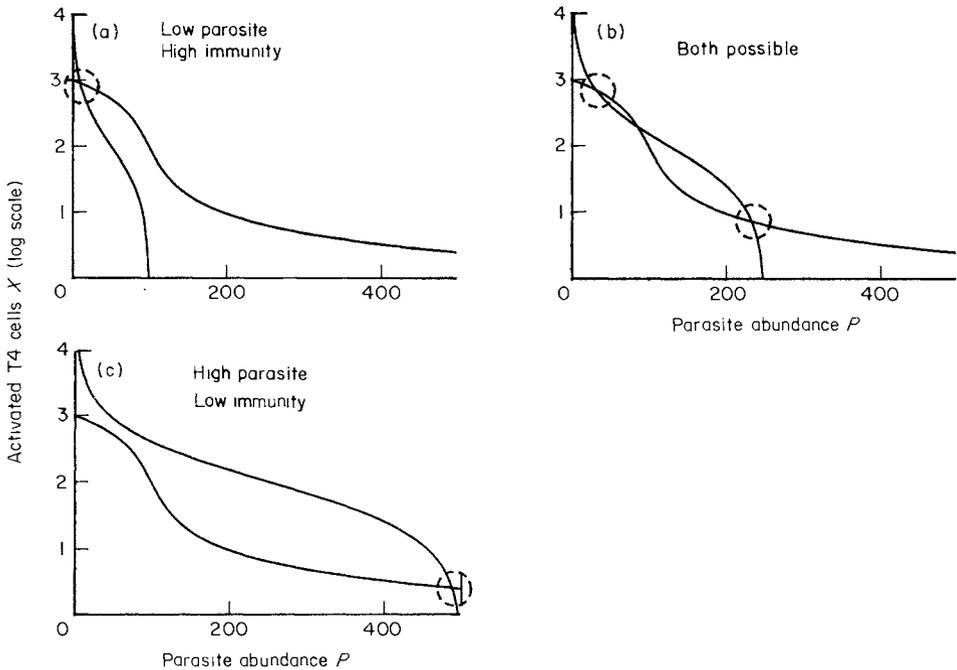


FIG. 36. Phase planes of the equilibrium density of activated T4 cells ( $X$ ) versus the equilibrium density of parasites ( $P$ ) in an individual host as predicted by eqns (47)–(49) in the main text. The two lines in each graph record the relationships predicted by setting eqns (48) and (49) equal to zero and substituting the equilibrium value for  $M$  derived from eqn (47). In the three graphs the rate of infection of the host,  $A$ , was varied from (a) 10 to (b) 25 to (c) 50 ( $\text{year}^{-1}$ ). Other parameter values  $\Lambda = 1$ ,  $\mu = 0.1$ ,  $\gamma = 0.01$ ,  $r = 0.2$ ,  $c = 0.0002$ ,  $\beta = 0.001$ ,  $d = 0.1$ ,  $s = 0.001$  (all  $\text{year}^{-1}$ ).

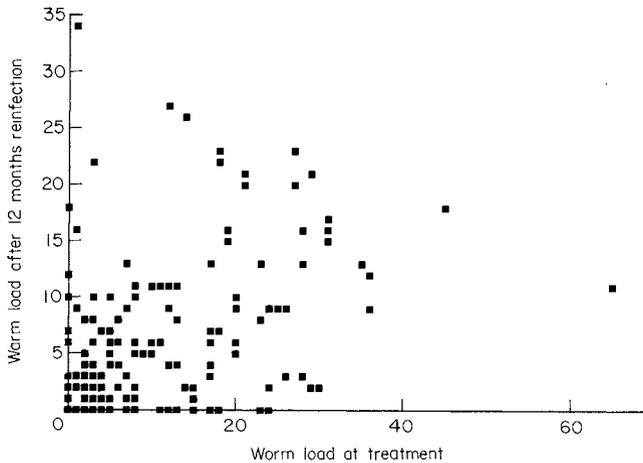


FIG. 37. Evidence for predisposition to heavy or light infection with *Ascaris lumbricoides* in a human community in India derived from studies of reinfection following chemotherapy to expel existing worm burdens. Expelled worms per person were recorded and worms acquired over a 12-month period of reinfection were measured via a second round of chemotherapy to induce worm expulsion (see Haswell-Elkins, Elkins & Anderson 1987). Each point denotes measures for a single patient. Non-parametric statistical analysis reveals a significant positive association between pre-treatment and post-reinfection worm loads in individuals.

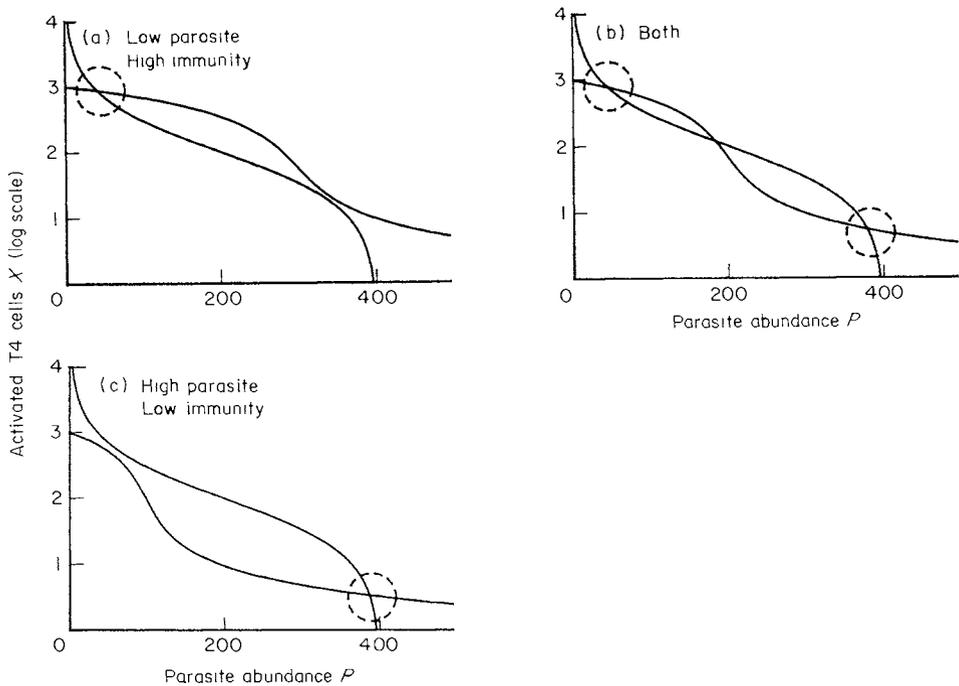


FIG. 38. Similar to Fig. 36 but recording phase planes for  $X$  and  $P$  as predicted by eqns (48) and (49) in the main text, with the infection rate  $A$  held constant but with the parameter that records lymphocyte recognition of parasite antigens,  $\gamma$ , varied from (a) high to (b) medium to (c) low values. Parameter values as for Fig. 36 with  $A=40$ .

Anderson 1987). There is much variation in the association between pre-treatment and post reinfection parasite loads but a non-parametric statistical test reveals a highly significant positive association between the two variables, suggesting predisposition to heavy or light infection (Spearman's rank correlation coefficient  $r_s=0.4256$ , d.f. = 175).

The likelihood of an individual developing strong or weak immunity to infection is also dependent on other parameters of the model. For example, as illustrated in Fig. 38, the parameter  $\gamma$  that controls lymphocyte recognition of parasite antigens has a major influence on whether or not strong immunity to infection will be acquired. If recognition is high such that lymphocytes are activated to mature at low parasite densities, strong immunity and low parasite burdens will result, and vice versa. It is probable that the degree of recognition is dependent on (amongst other factors) the genetic background of the host.

One use of simple models of the kind outlined above is to help guide research towards the development of better drugs or vaccines for parasite control. If multiple stable states exist, then theory suggests that immunization by parasite antigens that stimulate lymphocyte activation could, in principle, shift an individual from a state of low immunity and high parasite load, to a state of high immunity and low parasite burden. The model also suggests, however, that it will be difficult to fully protect against infection under conditions of continual exposure to the parasite as a direct consequence of the parasite's assumed ability to immunosuppress the host via deactivating mature lymphocytes. In this context the model also provides an explanation of why helminth infections are persistent

in character, where children in areas of endemic infection harbour worms for the majority of their lives. However, as in the case of the model of the interaction with HIV and the human immune system, the assumptions incorporated in eqns (47)–(49) are far too simple to accurately mirror the true complexities of the situation.

The two examples of the interactions between the immune system, HIV and helminth parasites, reveal a rich array of possible dynamical behaviours even with simple biological assumptions. An ecological approach to the study of such interactions, at the level of the individual organism within the host and the cells and factors that constitute the immune system, therefore appears to present many opportunities for improving our understanding of observed patterns of infection and disease, not only in populations of hosts, but also within individuals. In particular, simple models highlight the need to place much greater emphasis in research on infection and immunity, on the measurement and quantification of the rate parameters (e.g. birth, death and proliferation rates), and the functional dependencies between parasite and immune system variables, that determine dynamical behaviour. An ecological perspective has a lot to offer immunological research, but as yet this approach is not widely appreciated by those whose main research tools are molecular or biochemical in nature.

## CONCLUSIONS

The varied topics covered in the preceding sections suggest that many, if not most, of the central concepts in the study of epidemiology and transmission dynamics of infectious agents are essentially ecological in content and origin. The study of the interaction between host and pathogen therefore has many parallels with the investigation of two-species interactions that are much more familiar to the ecologist, e.g. predator–prey, competition, plant–herbivore or host–parasitoid.

Epidemiology has much to learn from ecological research, particularly with respect to the conceptual framework employed in the interpretation of observed fluctuations in the incidence of infection or disease. Far too much of current epidemiological research and teaching is based on a rather sterile statistical approach, which centres on description as opposed to the interpretation of the dynamic interplay between populations of hosts and infectious agents. Ideally, in the future training of epidemiologists, much greater emphasis should be placed on population biology, the lessons to be learnt from perturbation experiments (often initiated by the introduction of control measures) and the notions of reproductive success, density-dependent regulation and the stabilizing influence of heterogeneity. As such, a training in ecology can provide an excellent background for research on the transmission of infectious diseases. Epidemiologists enjoy many advantages over ecologists in pursuing these lines of research, due to the existence of well-developed reporting systems for monitoring population fluctuations, and the opportunities for experimentation presented by the necessity of control via mass vaccination, chemotherapy or behaviour modification. In addition, there now exists a well-developed theoretical framework for the study of the dynamics of infectious agent transmission and control, which parallels developments in the study of two-species interaction in general ecological study.

The value of this framework is not always well appreciated by those involved in the design of public health policy and programmes for the control of infection and disease in human communities. In part this is a consequence of the abstractly mathematical nature of the literature which has tended to become rather detached from its empirical base.

Incidentally, the same criticism can be aimed at some areas of ecological and evolutionary theory. Becker (1978), notes that of seventy-five papers on mathematical epidemiology published over the period 1974–78, only five contained any reference to empirical observations. It hardly needs stressing that if theory is to play a role in the solution of practical problems, whether in epidemiology or ecology, a much greater emphasis must be placed on data-orientated studies and the careful comparison of prediction with observation.

The criticism of too much theory and too little observation can justifiably be aimed at this paper. However, a major goal of simple theory is to further understanding of the interplay between the variables that determine the course of infection within an individual, and the variables that control the pattern of infection within communities of hosts. The new, and potentially exciting, application of ecological concepts in the study of the human immune system is but one example of such an approach. The medical epidemiologist's or immunologist's main concern is often the recondite biological detail that makes each infection or immune response unique. The new tools of molecular biology add a level of refinement in such descriptions unimagined even as recent as 10 years ago. In contrast, the aim of the population ecologist is to understand the basic similarities and differences in terms of: the number of population variables (and consequent equations) needed for a sensible characterization of the system; the typical relations among the various rate parameters (such as birth, death, transmission and cell proliferation rates); and the forms of the expressions that capture transmission or the interaction between immunological variables. In the absence of such a unified framework, each infection or immune response tends to develop its own, often arcane, literature. The problems of too simple a theoretical framework and the lack of comparison of prediction with observations are very real. However, to go from the observation of these difficulties to the belief that theory has little to offer the study of immunological responses or the design of programmes for the control of infection and disease is a mistake. Sensibly used, simple theory is no more, and no less, than a tool for thinking about things in a precise way. Its use in epidemiology is identical to that in the broader discipline of ecology.

Ecological research has much to learn from past work in epidemiology, especially at this current point in time with the growing focus of policy makers and the general public on environmental or 'green' issues. One lesson of particular importance concerns the organization of research, at both national and international levels, to monitor changes induced by human intervention. In epidemiology, it is common practice to put together national or international teams of researchers to monitor, for example, the impact of control intervention or genetic changes in infectious agent populations. The World Health Organization has played, and continues to play, a key role in this area, in collaboration with national health ministries, research institutes and university-based scientists. Problems tackled include the eradication of smallpox (achieved in October 1977; Fenner *et al.* 1988), monitoring genetic changes in the human influenza viruses and, more recently, charting the current pandemic of AIDS (Mann 1988). The data bases compiled by such co-ordinated national and international efforts provide a rich source of information which has greatly facilitated pure and applied research aimed at improving our understanding of observed pattern and the control of infection and disease.

Current concerns about global warming induced by apparent changes in the CO<sub>2</sub> concentration of the atmosphere and the depletion of the ozone layer over the two poles have stimulated international programmes of research on climatic change. These have been largely organized by meteorologists and atmospheric physicists plus chemists with

exemplary speed and great energy. These programmes will provide invaluable information on changes in CO<sub>2</sub> concentration in the atmosphere, alteration in climatic patterns and shifts in the depth and distribution of the ozone layer (Fiocco, Komlyr & Fia 1989). However, these climatic changes are important because of the impact they may have on the biological environment and, in particular, on ecosystem structure, function and productivity (with the associated implications for agricultural production worldwide). Furthermore, it may not prove possible in the short term (a decade or more) to detect underlying trends given the 'noise' inherent in the highly non-linear interactions between biological and physical variables in the global environment (Payette *et al.* 1989; Rossignol-Strick & Planchais 1989). Indeed, if chaotic behaviour is a feature of non-linear atmospheric and climatic systems the problem of detecting the 'signal' underlying the 'noise' may not be easily solvable.

In these circumstances, it is essential that the ecological community begins to organize research at national and international levels to provide a source of biological information to help monitor the impact of climatic change. This will require a different approach to that currently prevailing. By tradition, ecologists are not used to working within large interdisciplinary research teams focused on broad problems. They often prefer to study a particular species in a narrowly defined habitat given the constraints of limited resources for research. Furthermore, the notion of monitoring changes in population abundance over long time periods has become somewhat unfashionable, with the current emphasis on experimentation, environment manipulation or perturbation, and hypothesis testing. These trends are laudable but the current concerns over climatic change, combined with the dangers inherent in allowing too great an emphasis in international research programmes on the physical as opposed to the biological environment, argue that a change in attitude is required. This obviously requires confidence in the importance of an ecological approach to the study of the global problem, but more importantly it requires a reappraisal of the scale of research required. The ecological community must begin to 'think big' in terms of the response required to monitor and co-ordinate effective nationally or internationally based research programmes on the impact of climatic change on the biological environment. To achieve this end requires not only confidence in the value of the science but also a willingness to embrace new techniques in the study of species abundance and population interactions (e.g. remote sensing), to encourage physicists and engineers to develop new instrumentation for biological measurement on much larger spatial scales, to work within large interdisciplinary research teams and, most importantly, to be prepared to enter public and policy debate in order to influence the direction of science funding in favour of biological research.

The lessons learnt and the successes achieved by epidemiologists via co-ordinated national and international research programmes are to some extent a consequence of the perceived importance of infectious diseases (and the associated levels of research funding). Given the record of excellence in ecological research in the United Kingdom, in part initiated by the pioneering work of Tansley (1939), it is to be hoped that the British Ecological Society can play a leading role in stimulating and co-ordinating ecological research on national and international scales to sharpen our understanding of the potential impact of climatic change. There is no doubt of the importance of the problem, but what is needed at present is for the ecological research community to work together in assuring that our understanding of the biological implications does not lag behind that of physical changes in the global environment.

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## REFERENCES

- Anderson, R. M. (1979). The influence of parasitic infection on the dynamics of host population growth. *Population Dynamics* (Ed. by R. M. Anderson, B. D. Turner & L. R. Taylor), pp. 245–281. 20th Symposium of the British Ecological Society. Blackwell Scientific Publications, Oxford.
- Anderson, R. M. (1980). The dynamics and control of direct life cycle helminth parasites. *Lecture Notes in Biomathematics*, **39**, 278–322.
- Anderson, R. M. (Ed.) (1982). *Population dynamics of infectious disease agents: theory and applications*. Chapman and Hall, London.
- Anderson, R. M. (1988). Epidemiology of HIV infection: variable incubation plus infectious periods and heterogeneity in sexual activity. *Journal of the Royal Statistical Society, A*, **151**, 66–93.
- Anderson, R. M. (1989). Mathematical and statistical studies of the epidemiology of HIV. *AIDS*, **3**, 333–346.
- Anderson, R. M. (1990). The Kermack–McKendrick epidemic threshold theorem. *Journal of Mathematical Biology*, (in press).
- Anderson, R. M., Blythe, S. P., Gupta, S. & Konings, E. (1989a). The transmission dynamics of the human immunodeficiency virus type 1 in the male homosexual community in the United Kingdom: the influence of changes in sexual behaviour. *Philosophical Transactions of the Royal Society, London, B*, **325**, 45–98.
- Anderson, R. M., Crombie, J. A. & Grenfell, B. (1987). The epidemiology of mumps in the U.K.: a preliminary study of virus transmission, herd immunity and the potential impact of immunisation. *Epidemiology and Infection*, **99**, 65–84.
- Anderson, R. M. & Grenfell, B. T. (1986). Quantitative investigations of different vaccination policies for the control of congenital rubella syndrome (CRS) in the United Kingdom. *Journal of Hygiene (Cambridge)*, **96**, 305–333.
- Anderson, R. M., Grenfell, B. & May, R. M. (1984). Oscillatory fluctuations in the incidence of infectious disease and the impact of vaccination: time series analysis. *Journal of Hygiene (Cambridge)*, **93**, 587–608.
- Anderson, R. M., Jackson, H. C., May, R. M. & Smith, A. D. M. (1981). Population dynamics of fox rabies in Europe. *Nature*, **289**, 765–771.
- Anderson, R. M. & Johnson, A. M. (1990). Rates of sexual partner change in homosexual and heterosexual populations in the United Kingdom. *AIDS and Sex: An Integrated Biomedical and Behavioural Approach*. Oxford University Press, Oxford (in press).
- Anderson, R. M. & May, R. M. (1978). Regulation and stability of host–parasite population interactions. I. Regulatory processes. *Journal of Animal Ecology*, **47**, 219–247.
- Anderson, R. M. & May, R. M. (1979). Population biology of infectious diseases. I. *Nature*, **280**, 361–367.
- Anderson, R. M. & May, R. M. (1981). The population dynamics of microparasites and their invertebrate hosts. *Philosophical Transactions of the Royal Society, London, B*, **291**, 451–524.
- Anderson, R. M. & May, R. M. (1982). Directly transmitted infectious diseases: control by vaccination. *Science*, **215**, 1053–1060.
- Anderson, R. M. & May, R. M. (1983). Vaccination against rubella and measles: quantitative investigations of different policies. *Journal of Hygiene (Cambridge)*, **90**, 259–325.
- Anderson, R. M. & May, R. M. (1985a). Helminth infections of humans: mathematical models, population dynamics and control. *Advances in Parasitology*, **24**, 1–101.
- Anderson, R. M. & May, R. M. (1985b). Vaccination and herd immunity to infectious diseases. *Nature*, **318**, 323–329.
- Anderson, R. M. & May, R. M. (1988). Epidemiological parameters of HIV transmission. *Nature*, **333**, 514–519.
- Anderson, R. M. & May, R. M. (1989). Complex dynamical behaviour in the interaction between HIV and the immune system. *Cell to Cell Signalling* (Ed. by A. Goldbetter), pp. 335–352. Academic Press, New York.
- Anderson, R. M., May, R. M. & Gupta, S. (1989). Non-linear phenomena in host–parasite infections. *Parasitology*, **99**, 55–579.
- Anderson, R. M., May, R. M. & Gupta, S. (1990). The potential impact of chemotherapy, immunotherapy and vaccination on the transmission of HIV. *AIDS* (in press).
- Anderson, R. M., May, R. M. & McLean, A. R. (1988). Possible demographic consequences of AIDS in developing countries. *Nature*, **332**, 191–290.
- Anderson, R. M., May, R. M., Medley, G. P. & Johnson, A. M. (1986). A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS. *IMA Journal of Mathematics Applied in Medicine and Biology*, **3**, 229–263.
- Anderson, R. M., Ng, T., Boily, M. C. & May, R. M. (1989b). The influence of different sexual contact patterns

- between age classes on the predicted demographic impact of AIDS in developing countries. *New York Academy of Science*, **569**, 240–274.
- Anderson, R. M. & Thresh, J. M. (Eds) (1988). *The epidemiology and ecology of infectious disease agents*. Royal Society of London, London.
- Bacchetti, P. & Moss, A. R. (1989). Incubation period of AIDS in San Francisco. *Nature*, **338**, 251–253.
- Bailey, N. T. J. (1975). *The Mathematical Theory of Infectious Diseases and its Applications*, 2nd edn. Charles Griffin and Co., London.
- Beck, K. (1984). Co-evolution: mathematical analysis of host–parasite interactions. *Journal of Mathematical Biology*, **19**, 63–78.
- Becker, N. (1979). The uses of epidemic models. *Biometrics*, **35**, 295–305.
- Berkley, S., Okware, S. & Naamara, W. (1989). Surveillance for AIDS in Uganda. *AIDS*, **3**, 79–85.
- Bundy, D. A. P. (1988). Population ecology of intestinal helminth infections in human communities. *Philosophical Transactions of the Royal Society, London, B*, **321**, 405–420.
- Cherfas, J. (1989). AZT still on trial. *Science*, **246**, 882.
- Chesson, P. L. (1981). Models for spatially distributed populations: the effect of within-patch variability. *Theoretical Population Biology*, **19**, 288–325.
- Crofton, H. D. (1971). A quantitative approach to parasitism. *Parasitology*, **62**, 179–194.
- Crombie, J. A. & Anderson, R. M. (1985). Population dynamics of *Schistosoma mansoni* in mice repeatedly exposed to infection. *Nature*, **315**, 491–493.
- Desrosiers, R. C., Daniel, M. D. & Li, Y. (1989). HIV-related Lentiviruses of non-human primates. *AIDS Research and Human Retroviruses*, **5**, 405–474.
- Fenner, F., Henderson, D. A., Arita, I., Jezek, Z. & Ladnyi, I. D. (1988). *Smallpox and its Eradication*. World Health Organisation, Geneva.
- Fenyo, E. M., Albert, J. & Asjo, B. (1989). Replicative capacity, cytopathic effect and cell tropism of HIV. *AIDS*, **3** (suppl. 1), 55–512.
- Fiocco, G., Komlyr, W. D. & Fia, D. (1989). Is ozone destroyed during the Antarctic winter in the presence of polar stratospheric clouds. *Nature*, **341**, 426–427.
- Fisher, R. A. (1930). *The Genetical Theory of Natural Selection*. Clarendon Press, Oxford.
- Forsyth, K. P., Anders, R. F., Kemp, D. J. & Alpers, M. P. (1988). New approaches to the serotypic analysis of the epidemiology of *Plasmodium falciparum*. *Philosophical Transactions of the Royal Society, B*, **321**, 485–493.
- Frankland, H. M. T. (1954). The life history and bionomics of *Diclidophara denticulata* (Trematoda: Monogenea). *Parasitology*, **45**, 313–351.
- Gillespie, J. H. (1975). Natural selection for resistance to epidemics. *Ecology*, **56**, 493–495.
- Gupta, S., Anderson, R. M. & May, R. M. (1989). Networks for sexual contacts: implications for the pattern of spread of HIV. *AIDS*, **3**, 807–817.
- Haldane, J. B. S. (1949). Disease and evolution. *La Ricerca Scientifica Supplementa*, **19**, 68–76.
- Hamilton, W. D. (1980). Sex versus non-sex versus parasite. *Oikos*, **35**, 282–290.
- Hamilton, W. D. & Zuk, M. (1982). Heritable time fitness and bright buds: a role for parasites? *Science*, **218**, 384–387.
- Hassell, M. P. & Anderson, R. M. (1989). Predator–prey and host–pathogen interactions. *Ecological Concepts* (Ed. by J. M. Cherret), pp. 147–196. Blackwell Scientific Publications, Oxford.
- Hassell, M. P. & May, R. M. (1974). Aggregation in predators and insect parasites and its effect on stability. *Journal of Animal Ecology*, **43**, 567–594.
- Haswell-Elkins, M. R., Elkins, D. B. & Anderson, R. M. (1987). Evidence for predisposition in humans to infection with *Ascaris*, hookworm, *Enterobius* and *Trichuris* in a South Indian fishing community. *Parasitology*, **95**, 323–338.
- Hochberg, M. E., Hassell, M. P. & May, R. M. (1990). The dynamics of host–parasitoid–pathogen interactions. *American Naturalist* (in press).
- Hutchinson, G. E. (1978). *An Introduction to Population Ecology*. Yale University Press, New Haven.
- Jacquez, J. A., Simon, C. P., Koopman, J., Sattenspiel, L. & Perry, T. (1988). Modelling and analyzing HIV transmission: the effect of contact patterns. *Mathematical Biosciences*, **92**, 119–199.
- Johnson, A. M., Wadsworth, J., Elliott, P., Prior, L., Wallace, P., Blower, S., Webb, N. L., Heald, G. I., Miller, D. L., Adler, M. W. & Anderson, R. M. (1989). A pilot study of sexual lifestyle in a random sample of the population of Great Britain. *AIDS*, **3**, 35–142.
- Kahn, H. A. (1983). *An Introduction to Epidemiological Methods*. Oxford University Press, Oxford.
- Kanki, P. J., Alroy, J. & Essex, M. (1985). Isolation of T-lymphotropic retrovirus related to HTLV-III/LAV from wild-caught African green monkeys. *Science*, **230**, 951–954.
- Keymer, A. E. & Anderson, R. M. (1979). The dynamics of infection of *Tribolium confusum* by *Hymenolepis diminuta*: the influence of infective-stage density and spatial distribution. *Parasitology*, **79**, 195–207.
- Knox, E. G. (1980). Strategy for rubella vaccination. *International Journal of Epidemiology*, **9**, 13–23.
- Konings, E., Anderson, R. M., Morley, D. & Meegan, M. (1989). Rates of sexual partner change among two pastoralist southern nilotic groups in East Africa. *AIDS*, **3**, 245–247.
- Krebs, C. J. (1978). *Ecology, The Experimental Analysis of Distribution and Abundance*, 2nd edn. Harper and Row, New York.

- Law, R. & Watkinson, A. R. (1989). Competition. *Ecological Concepts* (Ed. by J. M. Cherrett), pp. 243–284. Blackwell Scientific Publications, Oxford.
- Lawton, J. H. (1989). Food webs. *Ecological Concepts* (Ed. by J. M. Cherrett), pp. 43–78. Blackwell Scientific Publications, Oxford.
- Levin, B. (1981). Periodic selection, infectious gene exchange and the genetic structure of *E. coli* populations. *Genetics*, **99**, 1–23.
- Levin, B. R. & Lenski, R. E. (1985). Coevolution in bacteria and their viruses and plasmids. *Coevolution* (Ed. by D. J. Futuyma & M. Slatkin), pp. 99–128. Sinauer Associates Inc., Sunderland, Mass.
- Macdonald, G. (1965). The dynamics of helminth infections, with special reference to schistosomes. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **59**, 489–506.
- Mann, J. (1988). Social, cultural and political aspects of AIDS: overview. *AIDS*, **2**, 5207–5208.
- May, R. M. (1977). Togetherness among schistosomes: its effects on the dynamics of the infection. *Mathematical Biosciences*, **35**, 301–343.
- May, R. M. (1975). *Stability and Complexity in Model Ecosystems*, 2nd edn. Princeton University Press, Princeton.
- May, R. M. & Anderson, R. M. (1978). Regulation and stability of host–parasite population interactions. II. Destabilizing processes. *Journal of Animal Ecology*, **47**, 249–287.
- May, R. M. & Anderson, R. M. (1979). Population biology of infectious diseases. II. *Nature*, **280**, 455–461.
- May, R. M. & Anderson, R. M. (1983). Epidemiological and genetics in the coevolution of parasites and hosts. *Proceedings of the Royal Society, London, B*, **219**, 281–313.
- May, R. M. & Anderson, R. M. (1987). The transmission dynamics of HIV infection. *Nature*, **326**, 137–142.
- May, R. M. & Anderson, R. M. (1988). The transmission dynamics of human immunodeficiency virus (HIV). *Philosophical Transactions of the Royal Society, B*, **321**, 565–607.
- May, R. M., Anderson, R. M. & McLean, A. R. (1988a). Possible demographic consequences of HIV/AIDS epidemics. I. Assuming HIV infection always leads to AIDS. *Mathematical Biosciences*, **90**, 475–505.
- May, R. M., Anderson, R. M. & McLean, A. R. (1988b). Possible demographic consequences of HIV/AIDS epidemics. II. Assuming HIV infection does not necessarily lead to AIDS. *Lecture Notes in Biomathematics*, **100**, 419–442.
- Medley, G. F. & Anderson, R. M. (1985). Density-dependent fecundity of *Schistosoma mansoni* infections in man. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **79**, 532–535.
- Noble, E. R. & Noble, G. A. (1976). *Parasitology: The Biology of Animal Parasites*, 4th edn. Lea and Febiger, Philadelphia.
- Nokes, D. J. & Anderson, R. M. (1988). The use of mathematical models in the epidemiological study of infectious diseases and in the design of mass immunization programmes. *Epidemiology and Infection*, **101**, 1–20.
- Payette, S., Filion, L., Delavaide, A. & Begin, C. (1989). Reconstruction of tree-line vegetation response to long-term climate change. *Nature*, **341**, 429–432.
- Peeters, M., Fonere, C., Huet, J., Bedjebaga, L., Ossari, S., Bussi, P., Copper, R. W. & Delaporte, E. (1989). Isolation and partial characterization of an HIV related virus occupying naturally in chimpanzees in Gabon. *AIDS*, **3**, 625–630.
- Prichard, R. K., Hall, C. A., Kelly, J. D., Martin, I. C. A. & Donald, A. D. (1980). The problem of anthelmintic resistance in nematodes. *Australian Veterinary Journal*, **56**, 239–251.
- Read, C. P. (1950). The ‘crowding effect’ in tapeworm infections. *Journal of Parasitology*, **37**, 174–178.
- Rossignol-Strick, M. & Planchais, N. (1989). Climate patterns revealed by pollen and oxygen isotope records of a Tyrrhenian sea core. *Nature*, **342**, 413–415.
- Schnittman, S. M., Psallidopoulos, M. C., Lane, H. C., Thompson, L., Baseler, M., Massari, F., Fox, C. H., Satzman, N. P. & Fauci, A. S. (1989). The reservoir for HIV-1 in human peripheral blood is a T cell that maintains expression of CD4. *Science*, **245**, 305–308.
- Southwood, T. R. E. (1981). Bionomic strategies and population parameters. *Theoretical Ecology* (Ed. by R. M. May), pp. 30–52. Blackwell Scientific Publications, Oxford.
- Southwood, T. R. E. (1977). Habitat, the template for ecological strategies. *Journal of Animal Ecology*, **46**, 337–365.
- Tansley, A. G. (1939). *The British Islands and their Vegetation*. Cambridge University Press, Cambridge.
- Taylor, L. R. (1961). Aggregation, variance and the mean. *Nature (London)*, **189**, 732–735.
- Taylor, L. R., Woivod, I. P. & Perry, J. N. (1978). The density dependence of spatial behaviour and the rarity of randomness. *Journal of Animal Ecology*, **47**, 383–406.
- Tinsley, T. W. (1979). The potential of insect pathogenic viruses as pesticidal agents. *Annual Review of Entomology*, **24**, 63–87.
- Ukkonen, P. & von Bonsdorff, Carl-Henrick (1988). Rubella immunity and morbidity: effects of vaccination in Finland. *Scandinavian Journal of Infectious Diseases*, **20**, 255–259.
- Varley, G. C., Gradwell, G. R. & Hassell, M. P. (1973). *Insect Population Ecology: An Analytical Approach*. Blackwell Scientific Publications, Oxford.
- Walker, D. (1989). Diversity and stability. *Ecological Concepts* (Ed. by J. M. Cherrett), pp. 115–146. Blackwell Scientific Publications, Oxford.