Group Report: Genetics and Evolution of Infectious Diseases in Natural Populations

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1 Introduction

At a meeting dominated by population dynamicists, it was perhaps inevitable that much of the discussion in the evolution sessions centred on what impact

genetic considerations might have on epidemiology in natural populations. The emergent view was that we simply don't know: there is relatively little epidemiological theory with explicit genetics and even less data. This is perhaps because theorists fear over parameterisation of already complex models, and empiricists are put off by the expense and need for even wider collaboration: counting individuals is easier than assaying genotypes. Nevertheless, there is great potential for those willing to try, and in the first part of this report, we attempt to summarise some of the possibilities.

In the second part, we focus on issues of interest to evolutionary biologists (and, we trust, others). Necessarily, the list is incomplete: discussing the evolutionary *et al.* over half the world's organisms in two days necessitates the odd oversight. We conclude with a tentative agenda, developed very much at the editors' prompting. This is at best a partial list of possibilities: current theoretical and empirical ignorance is so great that almost any detailed analysis of the evolutionary genetics of host-parasite interactions in natural populations would be an advance.

2 Genetics and epidemiology

2.1 Does genetic heterogeneity matter?

Initially conceived in the original Newton meeting programme as 'Other host population heterogeneities, particularly age structure and host immunity', our session had by the second circular attracted the word genetics to its title, but only in the final programme did 'Genetics and Evolution' emerge. Such treatment inevitably emphasised that explicit evolutionary genetics has largely been absent from the successful development of epidemiology over the past two decades. As Anderson and May (1991, p. 208) pointed out in the context of human disease '...there has been, in recent years, a growing amount of work on age-related, social and other heterogeneities in host populations, [but] the possibility of genetic heterogeneity continues to be neglected in most epidemiological studies... This is understandable, because there is not much concrete evidence on which to base such studies'. We note that this lamentable state of affairs is, if anything, more acute for wild populations. Variation in disease resistance in domesticated and laboratory animals is well documented (e.g. Wakelin and Blackwell 1988, Kloosterman *et al.* 1992), as is genetic variation in resistance to pathogens within crop plants (e.g. Burdon and Jarosz 1990). Those studies that have attempted to look in natural populations of pathogen and hosts have documented genetic variation in interactions (Parker 1985, 1986, Burdon 1987, de Nooij and van Damme 1988, Alexander 1989, Burdon and Jarosz 1991, Fritz and Simms 1992, Alexander *et al.* 1993, Alexander and Antonovics, submitted); as an example, interactions between aphids and two of their natural enemies are described in Box 1. The

Box 1. Genetic variability in resistance and virulence in a natural system.

Experimental studies of the genetics of interactions between pea aphid and their most common parasitoids and fungal pathogens provides evidence of genetic variation within an insect species in resistance to its natural enemies. Within a single population, susceptibility to the parasitoid wasp *Aphidius ervi* ranged from 0–90% among different clones (Figure 1a; Henter and Via submitted). Within the same set of aphid clones, susceptibility to the dominant fungal pathogen (*Pandora neoaphidus*) ranged from 22–79% among different aphid genotypes (Hural 1994, Hural and Via in preparation). This genetic variability provides the raw material in this aphid population for the evolution of resistance to both of these natural enemies. Moreover, experiments have also revealed significant genetic variability within both the fungal population (Hural 1994) and the wasp in the same field (Figure 1b; see also Henter submitted). Therefore, genetic variation is locally available in all the participants in a potential three-species coevolutionary interaction.

absence of data is especially acute for wild vertebrates; indeed the greater emphasis on genetics in plant compared with animal epidemiology is perhaps in part due to the greater empirical base, presumably as a consequence of the relative ease of genetic analyses.

In what sense might genetic variability be unique relative to other heterogeneities considered by epidemiologists? How might the results of models differ if realistic estimates of genetic variability were included? When pressed, none of the group could come up with a convincing example of the failure of an epidemiological model that was definitely attributable to an absence of explicit genetics. Nevertheless, the general view was that this reflects the absence of genetic data as much as (or even more than!) the success of epidemiological models. The following areas emerged in discussion as potentially of interest to epidemiologists.

Epidemiological dynamics can depend on genotype

Numerous theoretical studies have demonstrated that heterogeneity of any sort can have major implications for population dynamics (e.g. Anderson and May 1991). However, relatively few data are available which combine population and genetical data. One such study is summarised in Box 2; here genetic composition of experimental populations had both qualitative and quantitative effects on the population dynamics observed.

An unexplored possibility is the role that genetic heterogeneity may play in stabilising host-pathogen dynamics in the wild. From a recent model which in-

Box 2. Silene-Ustilago: an example of the impact of host genetics on epidemiology of disease in natural populations.

Silene alba is a short-lived dioecious perennial found in ruderal habitats. The anther-smut *Ustilago violacea* parasites some populations of *S. alba*, such that diploid teliospores are produced in the anthers of infected flowers. These spores are transmitted to new hosts via insect pollinators. Newly diseased flowers appear between three weeks and two months after infection, when the fungus has grown through the plant and into developing buds. Plants often become systematically infected, so that by the following year all flowers are diseased resulting in complete sterility. There is no evidence that infected plants recover, and on average, disease-induced plant mortality is negligible.

The basic model for host-pathogen dynamics with frequency-dependent disease transmission applied to this system can be written as (Thrall and Jarosz submitted):

$$X_{t+1} = \frac{b_0}{b_1 N_{t+1}} + (1-d)\left(1 - \frac{BY_t}{N_t}\right) \quad (2.1)$$

$$Y_{t+1} = Y_t(1-d)\left(1 - \frac{BX_t}{N_t}\right) \quad (2.2)$$

where d is the host death rate; $b_0/(b_1 N_{t+1})$, the density dependent per capita rate of reproduction, with b_0 the maximum host reproductive rate, and b_1 a constant; X_t, Y_t, and N_t are respectively the number of susceptible hosts, infected hosts and total population size at time t; $\beta Y_t/N_t$ the frequency dependent rate at which individuals become infected, with β as a measure of the effectiveness of transmission. Parameter values were estimated from data other than that used to test the model.

When natural host mortality was low, the model predicted coexistence of host and pathogen in susceptible populations, but in resistant populations the pathogen was lost (Figure 2). When natural host mortality was high, the pathogen was lost from the host population with little effect of host genotype.

These predictions were tested as follows (Thrall and Jarosz submitted). Experimental populations were established in pots on an abandoned golf course. A proportion of the pots were planted with diseased or healthy plants, with the remainder left available for seed colonisation. Following establishment of the pots, seedling establishment and disease transmission was allowed to occur naturally. Populations were established from crosses between parents of known susceptibility (determined from greenhouse inoculations and independent field trials). Data from two years are now available (Figure 3). The initial dynamics of susceptible populations was qualitatively different from those of resistant populations, consistent with the model predictions.

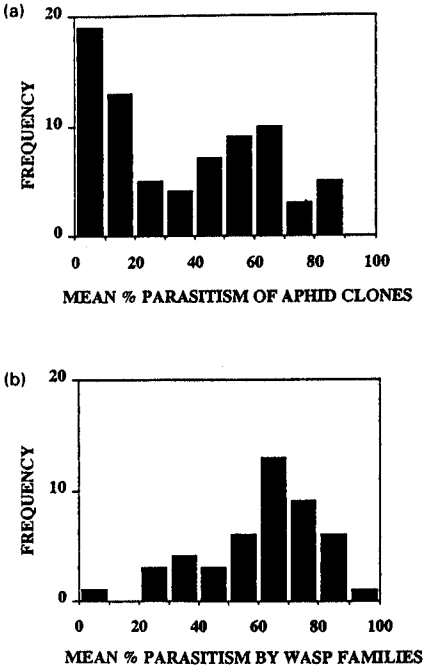

Figure 1. Genetic variation in a natural host-parasite system. (a) Aphid susceptibility to parasitism. Data are parasitism rates for each of 64 aphid clones, as the averages of five trials for each clone. Each trial consisted of exposing 20 juvenile aphids of each clone to a single wasp that had been chosen at random from a laboratory colony established from wasps collected in the same field as the aphids. After 24 hours of exposure, each wasp was removed, and parasitised individuals were scored eight days later. (b) Parasitism by wasp parasitoid families. Female progeny from a half-sib mating design of field collected wasps were allowed to parasitise groups of aphid nymphs of single moderately resistant clone, using the exposure protocol of (a) (both figures redrawn from Henter and Via submitted).

corporates quantitative genetic variation in a predator-prey model, Saloniemi (1993) derives stability criteria which are a function of the magnitudes of genetic variation in phenotypic characters that mediate the interaction between predator and prey. Stability was enhanced as genetic variation in these characters increases in both predator and prey. Other model produce a qualitatively similar picture in host-pathogen systems (Antononvics in press). This is in interesting contrast to the view of several theoreticians that incorporating demographic factors into coevolutionary models can make complex dynamical behaviours more likely (Anderson and May 1991 p. 643, Frank 1993).

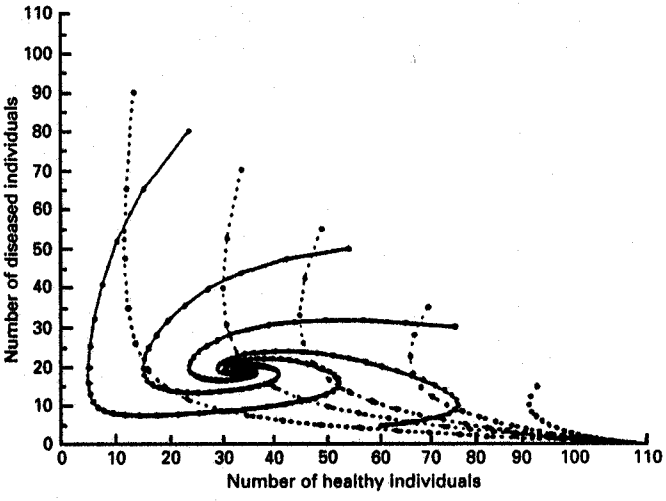

Figure 2. Dynamics of hosts and parasites from equations (1) and (2). Dashed lines, resistant hosts; solid lines susceptible hosts (from Thrall and Jarosz (submitted), who give parameter estimates).

Genetic heterogeneity may generate epidemiological patterns presumed to have other causes

Age dependence in the force of infection (rate that a susceptible of age a will acquire an infection at that age), typical of many human diseases such as measles, is usually viewed as a consequence of age-specific changes in the degree of mixing and contact within and among age classes (e.g. school attendance). However, as Anderson and May (1991, Chapter 10) have emphasised, genetic heterogeneity in response to infection is capable of generating the same pattern. More susceptible individuals would, on average, become infected at younger ages than less infectable individuals who might suffer disease at later stages. Genetic differences are clearly not the only heterogeneity which might generate such a pattern, but the general point is clear: they might. If such heterogeneities are relevant, estimates of the level of herd immunity required to eradicate the disease are affected, with implications for the design of vaccination programs (Anderson and May 1991). It would be interesting to know whether similar age dependencies exist in natural populations with very different social structures, and if so, whether there was any genetic basis. More generally, investigations of the role of host genetic diversity in generating epidemiological phenomena in wildlife populations is likely to be fruitful. Invasive or destructive investigations of the causes of aggregation in macroparasite populations, for example, may be more tractable in natural populations.

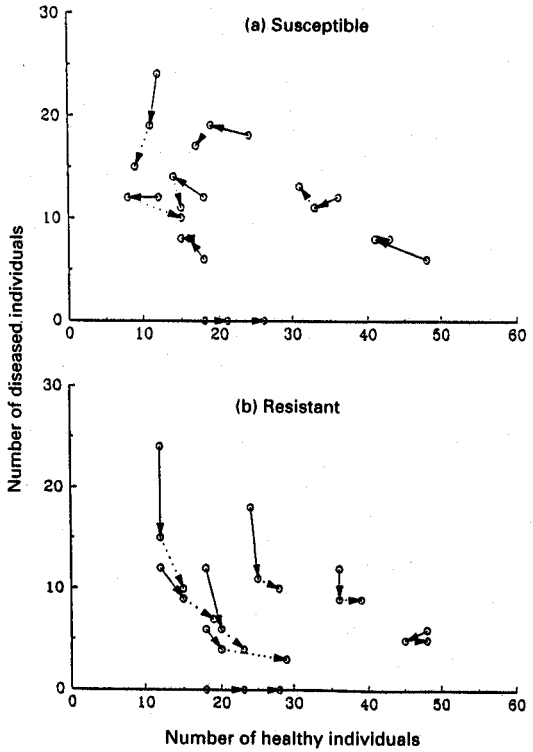

Figure 3. Year to year transitions in numbers of healthy and diseased individuals for population cages (1990–1992) (from Thrall and Jarosz, submitted).

Pathogenicity can be influenced by pathogen genotype

It is well known that for many human diseases there is often a poor correlation between the presence or level of infection and the severity of disease (e.g. Marsh 1992). The extent to which this is due to differences in parasite genotype is in some cases controversial (e.g. Marsh 1992, Day *et al.* 1992), but in other cases there seems little doubt. For example, *Toxoplasma gondii*, an important human pathogen particularly in AIDS patients, is found in many vertebrates and strains can be characterised as either virulent or avirulent by their effects on susceptible mice. A recent genetic analysis of 28 strains taken from humans (both with and without AIDS) and various domestic animals found that virulent strains ($n = 10$) had essentially the same genotype, whereas nonvirulent strains were polymorphic (Sibley and Boothroyd 1992). As population genetic analyses of parasites become more common, we expect the influence of parasite genetics on the outcome of parasitic infections to be more obvious.

Parameters of epidemiological models can evolve rapidly if they are genetically variable

Most characters examined in quantitative genetic analyses have been found to be genetically variable. Genetic variation in behaviours and physiological traits influencing transmission thus affords the potential for evolutionary change in key parameters of epidemiological models.For example, both the virulence of the myxomatosis virus and the resistance of the rabbit to the virus have evolved during the relatively short time in which the two species have been interacting in Australia. To what extent a knowledge of the genetic variability in both virulence and resistance in this system would make accurate predictions about the future ability of the virus to control the rabbit remain to be seen (Dwyer *et al.* 1990, and see below). Nonetheless, the general point is uncontroversial: genetic variation (in hosts and parasites) allows evolution (and coevolution). The role of genetic diversity in shifting host-parasite relationships is relevant to inbred domestic animal populations as well as dwindling natural populations, such as black-footed ferrets or large felids (e.g. Antonovics 1990).

The outcome of biological control measures might be affected by host-parasite coadaptation

Genetic variability in host-parasite or host-pathogen interactions may be relevant to biological control. It is known, for example, that the source of material used in biological control programs can influence the outcome of an introduction (Hopper *et al.* 1993). A dramatic example of the importance of considering the source of an introduced natural enemy is provided by the introduction to Australia of an herbivore to consume the floating weed *Salvinia molesta* (Room *et al.* 1981). After failing to control the weed with herbicides, considerable effort was initially made to release a beetle species collected from northern South America and Trinidad where it was known to consume a closely related species (*S. auriculata*). These introductions were completely unsuccessful. However, collections of the same beetle species from a site in Brazil where *S. molesta* was used as a host were successful. Thus, attention to the fact that parasites are likely to be locally adapted to their hosts (Lively and Apanius, this volume, Burdon and Jarosz 1991) can dramatically improve the chances of a successful introduction. Local genetic adaptation of species to various aspects of their environment may also be important with respect to conservation issues and maintenance of biodiversity given small and fragmented populations (e.g. Antonovics 1990).

2.2 The relationship between evolutionary genetics and epidemiology

In many ways, the genetical problem of characterising conditions for the persistence of alternative alleles at a single locus in a closed population closely

parallels the ecological problem of understanding the coexistence of interacting species in a community, and selectively maintained genetic monomorphism is akin to interspecific dominance and exclusion. For simplicity, genetical models are often cast as single-locus haploid systems: these are, in effect, models for interacting species. For example, McLean and Nowak's (1992) model of the evolution of AZT-resistance in HIV populations within a single individual is effectively a two-species competition model, with sensitive and drug resistant genotypes competing for CD4+ cells, fitnesses defined in terms of population growth rates of the two types, and with each type maintained by mutation from the other state. Such models suggest the idea that incorporating evolutionary genetics into epidemiology need not involve much new theoretical baggage: ideas developed more or less independently from evolutionary and ecological models might be mutually illuminating.

For instance, consider the following. Genetic explanations for polymorphism in haploid systems usually invoke frequency-dependent selection. Ecological explanations for coexistence instead concentrate on the relative strengths of intraspecific and interspecific density-dependent interactions (which can lead to frequency-dependence). These interaction strengths in turn often reflect the interplay of niche differentiation (in a very broad sense) with environmental heterogeneity and patchiness. In the pathogen-pathogen-host model of Hochberg and Holt (1990), for example (see Begon and Bowers, this volume), where individuals infected with one strain cannot be infected by the other, there is basically exploitative competition for a single limiting resource, so that the species able to persist at the lower resource (= susceptible host) density excludes the other species. What factors, then, could promote the coexistence of pathogen genotypes? Community ecologists have compiled a lengthy laundry list of possibilities, appropriate to different ecological situations. A few of these, tailored to the multi-pathogen-host system, are as follows: (i) One species could use the other as a resource. In the Hochberg-Holt system, coexistence can occur if the inferior exploitative competitor is able to invade hosts already occupied by the superior exploitative competitor, and supplant the latter; (ii) The host population may be heterogeneous, so that pathogen demes differ in their ability to utilise subsets of hosts. Anderson and May (1991, pp. 622–624) present an interesting model in which the host has a strain-specific immune response which fully protects it in the future against that strain, but not against the other strain. This permits two pathogen strains to coexist on one host, essentially because each has an exclusive resource not available to its competitor. On the flip side, use of immunosuppressive adaptations by a parasite strain to infect a host may allow unrelated parasites to colonise the host population. The recent outbreak of pneumocystis pneumonia in HIV-infected people is a poignant example. Other possibilities for coexistence of two strains due to host heterogeneity

include localised dispersal coupled with local superiority in particular habitat patches; differential attacks as a function of age; and, of course, appropriate genetic variation in the host. The aggregated distributions typical of parasitic helminths are crucial in determining coexistence and may allow two or more species to coexist in the same host population (Dobson 1985).

Thus considerable value can probably be gained from more explicit attempts to interpret the dynamics of evolving host-parasite systems using the perspectives of community ecology. There are, however, some obvious differences in the scope of the two classes of models. The main difference is in the details (albeit often crucial) of the transmission dynamics: species breed true, whereas genotypes beget unlike genotypes. Indeed, evolutionary models are perhaps best viewed as ecological models with the addition of complex mating dynamics. Consider for instance the host-host-pathogen model of Begon and Bowers with host self-regulation. This is perfectly reasonable as a community model, for different species often do have largely non-overlapping resource requirements. It is not likely that this model structure will apply directly to very many examples of within-host genetic variation: most genetic variants differ in a few respects from their conspecifics, but not so much as to be regulated completely independently. Moreover, genetic models in which one tracks the fates of a few competing host and/or parasite strains are literally only appropriate for major genes, and as a kind of scaffolding needed when using ESS approaches. Thus, while a simple one-locus approach provides a convenient way to begin to explore the role of genetics in epidemiology, the analogy with ecological models blurs when considering systems with multilocus or quantitative genetic variation, or where inheritance of traits and associated relative fitness' is not just the mid-point of parental values (e.g. where there are sex differences in reproductive success [fecundity selection], heterozygote advantage etc.).

The extent to which one or two locus models are too restrictive to provide an accurate description of either dynamics or equilibria in host-pathogen systems remains an open question, again principally because of the paucity of data. We note, however, that in models of evolution in spatially patchy environments, classical one-locus genetic models (e.g., Levene 1953) are a special case of more general quantitative genetic models (Via and Lande 1985). The one-locus model predicts the maintenance of genetic variation in a spatial patchwork, while the quantitative genetic model does not. This is because the one-locus case cannot produce the wide range of genetic and phenotypic values (and consequently the range of parameter values) that can be utilised in a quantitative genetic model (see also Dickinson and Antonovics (1973) p. 260). This means that there is a limitation on the degrees of freedom for evolutionary change in the simpler models. Thus, the results of the one-locus models in this case are actually constrained by the simplicity of the genetic

assumptions (other assumptions are the same as in the quantitative genetic models of Via and Lande 1985). This is a possibility that should also be considered as genetics are incorporated into epidemiological models, though which approach is the preferable is unclear (and contentious!). Nevertheless, where evolutionary studies of parasites have been attempted (e.g. the evolution of virulence), models have been largely devoid of explicit genetics. It is not yet obvious whether this matters much, again, because nobody has tried to find out.

2.3 Genetical theory devoid of epidemiological considerations

Although discussion was focused on what genetical considerations might bring to epidemiology, a recurring theme was that an explicit consideration of the ecological dynamics of host-parasite systems may sharpen one's understanding of evolution in these systems, and for several distinct reasons.

First, the dynamic stability – or instability – of a host-parasite interaction can constrain the potential for selection to act. As an extreme example, the American chestnut tree was devastated by a blight early in this century. The chestnut's numbers were reduced to such low densities that the tree went extinct (at least as breeding adults) over large areas, and is now found only in scattered pockets, mainly near the edge of its previous range. Any genetic variation initially present that could potentially have fostered an increase in resistance was simply not given the opportunity to become expressed, given the speed and severity of the epidemic. The ecological conditions that permit a lineage to persist define the arena within which evolution can occur. In the case of the chestnut, one could easily imagine that the rate of transmission of the blight might have been less, had the chestnut been more patchily distributed in the forest; this might have permitted enough individuals to remain for natural selection to operate.

Population dynamics might also indirectly govern the rate or direction of evolution in less extreme cases. The effective size of a population scales the standing crop of variation that can be maintained in the face of drift, and governs the rate at which new variation is generated via mutation. Given population fluctuations, effective population size is approximately the harmonic mean population size, which is dominated by population lows. Unstable host-pathogen interactions leading to recurrent population crashes may thus influence the amount of variation available for selection.

Second, formulations of fitness in terms of epidemiological and ecological parameters allow simultaneous analysis of frequency- and density-dependence in selection. In particular, Anderson and May (1991, p. 643) emphasise that epidemiological models can be used to develop fitness functions explicitly reflecting the ecology of the populations. They present an example of how

incorporating density effects into a coevolutionary model makes complex dynamical behaviours (cycles/chaos) more likely. This general protocol permits a richer interpretation of the selective forces impinging on the interacting populations (relative to the somewhat abstract relative fitness coefficients of 'gene-for-gene' models). The parameters of a well-specified model comprise those traits among which one might seek trade-offs (e.g., in developing an ESS model) or genetic covariances (in formulating a quantitative genetic evolutionary model).

2.4 Putting it all together

Perhaps the most striking feature of efforts to model evolution in host-pathogen systems is the tendency to add genetics and/or fitness functions to an existing ecological framework, or to add epidemiology to existing genetical models. There may be value in attempting to develop models incorporating both population and evolutionary dynamics from the start (e.g. Anderson and May 1991, Frank 1993, Nee and May 1993).

3 Evolutionary issues

3.1 Can parasites maintain genetic diversity?

The idea that coevolution of hosts and parasites is responsible for the maintenance of host genetic diversity (e.g. reviewed by Lively and Apanius in this volume) has received little direct empirical support for disease-associated direct selection in natural populations of vertebrates, though there is some evidence from human populations (e.g. Allison 1954, Hill *et al.* 1991) and laboratory-maintained populations derived from wild-caught animals (e.g. Wassom *et al.* 1973). The paucity of examples from wild populations may arise because there are still comparatively few studies with good measures of fitness components for large numbers of individuals (Clutton-Brock 1988), and even fewer involving both genetical and parasitological screening. The only non-human animal example of which we are aware is that of Soay sheep on St Kilda (Box 3), and there is a clear need for similar detailed studies in other wild animal populations. Furthermore, even in the case of the relatively well studied Soay sheep, the population dynamical consequences of parasite-induced genetic polymorphism are poorly understood. In plants, there is abundant circumstantial evidence that such polymorphism exists (e.g. Burdon 1987, Fritz and Simms 1992), although precise quantification of forces acting on resistance (or virulence) genes in any particular system is lacking. There is a need for studies that assess whether such polymorphisms are transient or stable (either locally or, when pathogens are widely dispersed, on a larger scale), and whether they are present because of selection on correlated features of the organism.

Box 3. Parasite-associated genetic polymorphism in wild sheep.

A feral population of Soay sheep has existed on the island of St Kilda, Scotland, for over 1000 years. The population follows an apparently stable limit cycle (Grenfell *et al.* 1992), where differences in mortality during over-winter population crashes (Clutton-Brock *et al.* 1991, Grenfell *et al.* 1992) was associated with gastro-intestinal nematode parasitism (Gulland 1992, Gulland *et al.* 1993). Extensive genetic screening has been carried out using polymorphic protein loci and polymorphic microsatellite loci. At the adenosine deaminase protein locus (a biallelic protein screened from leucocyte lysates), significant differences in survival in three consecutive population crashes (1986, 1989, 1992) were associated with significant differences in gastrointestinal worm burdens (as measured by faecal egg counts). Homozygous individuals suffered higher mortality (Figure 4) and had higher faecal egg counts. The explanation of these correlations remains speculative. However, ADA-associated immunocompetence has been reported in a number of domestic animals, and adenosine deaminase deficient genotypes in humans have abnormal T and B lymphocyte production and hence abnormal immune responses. Indeed, the Newton meeting coincided with press reports of the first use of human gene therapy in the UK, which was targeted at the ADA locus and immune deficiencies.

It remains to be seen if there are any population dynamical consequences of the ADA heterozygote advantage.

3.2 Can parasites maintain diversity-generating strategies?

A related issue is the role of parasite-mediated selection in the maintenance of sex, recombination and outcrossing (Lively and Apanius this volume). There is a clear need to distinguish these strategies in empirical and theoretical tests. In particular, the latter may be most challenging for the parasite view, as selfing can generate variable offspring, especially initially.

Several lines of theoretical work were suggested (see also Lively and Apanius this volume). First, even if parasites are involved, other environmental features may also play a role and the effects of any interactions is unclear in the absence of crowding or resource limitation. For example, parasites may not always apply significant selection pressures. Second, we have little theory about what sort of parasites should be involved (e.g. their life cycles, generation length, virulence, reproductive mode, endemic or epidemic etc). Third, under what conditions would parasite imposed selection actually act to increase levels of clonal diversity, rather than favour sex or outcrossing.

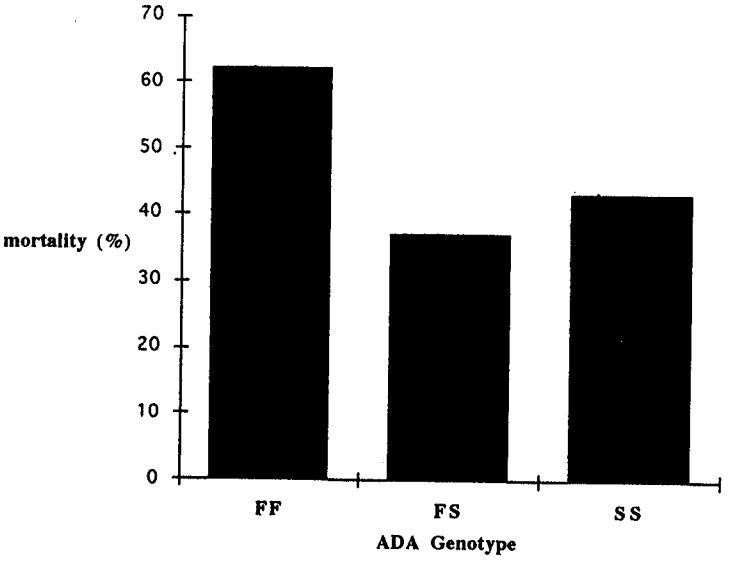

Figure 4. Percentage mortality of Soay sheep of different ADA genotypes average across three consecutive population crashes. $X^2 = 9.58$, $p < 0.01$. (Redrawn from Gulland *et al.* 1993).

Finally, what factors should influence parasite sexual strategies?

In addition to the types of empirical tests reviewed by Lively and Apanius (this volume), other, possibly stronger tests should be possible. For example, parasites may act to increase recombination in the genome in general, but the costs of recombining other, well-adapted gene complexes must be quite high. Thus, parasites may act to increase recombination in 'hot spots'. These would be areas of the genome that are relevant to parasite defence, such as the MHC complex. Other areas should remain relatively untouched. The somatic 'recombination' seen in some vertebrate immune systems might be a pinnacle of such 'hot spots'. As a caveat, though, recombination in specific areas may not be related to parasites; rather, other areas of the genome might be conserved, as for example, in mimicry patterns.

Selection experiments should offer powerful tests. Artificial selection can alter recombination rates (Brooks 1988), but whether parasites could exert such pressures remains to be shown. Parasites may also act to increase outcrossing rates in sexual organisms. In general, there might be a relationship between mechanisms that ensure outcrossing and risk of parasitism. This might be an explanation for outcrossing beyond the avoidance of inbreeding depression; in fact, inbreeding depression may be a consequence of the genetic load imposed by parasites selecting for outcrossing.

Parasites may play a role in the evolution of breeding systems (e.g. Read

1991). Mate choice may be a way to confer parasite resistance on offspring. For example, mate choice in mice generates larger than expected frequencies of heterozygotes at the MHC locus (Potts *et al.* 1991). This may well be a mechanism of conferring parasite resistance if heterozygotes express enhanced resistance. Also, multiple mating in polyandrous systems may increase the genetic diversity of offspring. An interesting case is provided where offspring stay to form social groups, such as in colonial invertebrates, social insects or social mammals (Hamilton 1987, Sherman *et al.* 1988). Increased genetic variation within such groups has demonstrable effects on trypanosome infections in colonies of social insects (Shykoff and Schmidt-Hempel 1991). These castes also provide examples of populations where spatial structure is closely related to genetic structure. This should profoundly affect the dynamics and evolution of the host-parasite system and may provide good examples to test ideas about the interaction of genetics, space and selective pressures. Clone experiments and field studies would allow investigation of the extent to which parasites influence the evolution of sociality (Freeland 1976, Hamilton 1987).

3.3 Host resistance

Our understanding of the mechanistic basis of host resistance – defined broadly to include any trait likely to mitigate the effects of parasitic infection – is inversely related to taxonomic diversity. The genetic and physiological basis of resistance is best understood in mammals and a few crop plants, less well characterised in other chordate classes and only dimly understood in the speciose invertebrate and dicot plant phyla. Certain modes of resistance are clearly widespread, such as phagocytosis and self-nonself recognition, while other modes, like somatic evolution, are probably restricted to particular phylogenetic lineages. Traditionally, the field of comparative immunology has focused on identifying homologous components of the mammalian immune system in other taxa, primarily analysis of nucleotide sequence similarity of cognate genes (e.g. Lambert *et al.* 1989). As a consequence, our functional understanding of parasite resistance modes in the majority of host organisms has suffered. Notable exceptions include the molluscan (Noda and Loker 1989), acarine (Burgdorfer *et al.* 1991) and arthropod (Schaub 1992) vectors of human parasites where resistance mechanisms receive the same vigor of investigation devoted to mammalian immunity. The artificial barrier between 'biomedical' and 'basic biological' investigations erected by funding agencies inhibits cross-fertilization between evolutionary ecology and invertebrate and vertebrate immunology.

Currently, there is no synthetic theory of resistance which has the potential to explain, much less predict, which particular resistance mechanisms are likely to evolve in any particular circumstance. For example, when are specific immune responses favoured over non-specific responses, or why do

particular modes of resistance overlap in a seemingly extravagant duplicity of effort? Such a theory would be a major step towards understanding the natural history of resistances mechanisms, about which we currently know a great amount of detail but have few ultimate explanations. It would also have tremendous practical significance: enormous redundancy in mechanisms is apparently a feature of host resistance, with a plethora of fixed and facultative responses involved. Determining which of these are actually important in controlling a particular infection, and which are epiphenomena perhaps important in other infections, might be easier if we had an adaptive theory of resistance. In contrast to cellular and molecular studies of host responses, evolutionary understanding requires an emphasis on function and process rather than structural detail. The inroads made by other disciplines attempting to understand the design principles of an immune system are illustrated by models of immunoregulation which attempt to distil the wealth of detail into simple functions (e.g. Schweitzer *et al.* 1993), and the appreciation that self-nonself recognition is a cognition problem (Cohen 1992).

Developing ideas about the evolution of resistance is likely to require some notion of the conditions under which non-specific responses are inadequate, and of the costs and benefits of particular resistance mechanisms. Data on the fitness costs of resistance are also are likely to be relevant to ecological dynamics (e.g. Frank 1993), evolutionary dynamics (e.g. the rate and magnitude of evolving resistance, as well as other traits affected by the costs of parasitism), and the evolution of pathogen virulence (see below).

Relevant data are scanty. It seems likely that resistance to parasitic infection will be associated with reductions in other components of fitness, but supporting evidence is largely indirect. One argument is that it is difficult to see why else hosts susceptible to extant pathogen genotypes would exist in a population. Indeed, this is probably why susceptible *Escherichia coli* are maintained in phage-infected populations (Levin and Lenski 1985). But there are other reasons why susceptibles may be maintained in a population. One is deleterious mutations at loci involved in resistance. Another is that continuing coevolution may mean that counter-adaptations are constantly arising in parasite populations, and lack of resistance is perhaps a consequence of time lags. Nevertheless, it difficult to imagine that the energy and material produced during a immune response in vertebrates is not without cost; presumably it is this which necessitates the need for clonal expansion and acquired immunity, rather than innate pre-emptive immunity, if indeed hosts have the potential to respond to any antigen.

Other evidence for resistance-associated costs include: the existence of autoimmune conditions and pathology due to host effector mechanisms rather than the pathogen-damage (e.g. schistosomaisis, hepatitis B, elephantaisis, acute intestinal responses to nematode infections (Behnke *et al.* 1992) and

of parasites which exploit defenses used by hosts against other pathogens (e.g. *Leishmania* spp., HIV); the generally negative effects of malnutrition on immunocompetence; and the effects of extra reproduction on susceptibility to disease (e.g. Festa-Bianchet 1989, Norris *et al.* 1994). More specifically, snails refractory to trematode infection have lower fecundity than unexposed controls (Minchella and LoVerde 1981), which might represent fitness costs associated with facultative host responses (Keymer and Read 1991). In addition, relationships between MHC haplotype and growth and fecundity parameters have been reported (Bonner 1986, Dietert *et al.* 1990), which suggests that this locus controls more than antigen presentation to lymphocytes, and artificial selection for increased resistance in domestic and laboratory animals often results in reduced fecundity, body size or life expectancy (e.g. Brindley and Dobson 1981, Siegel *et al.* 1983, Kloosterman *et al.* 1992). These results suggest a fundamental trade-off between allocating nutritional resources to lymphoid tissue (and host defence) or to reproductive component. Whether trade-offs revealed by such selection experiments persist in the long term is difficult to ascertain. We are only aware of one selection experiment on a natural host-parasite system (albeit maintained in the laboratory); here, resistance was again associated with decreased fitness in the absence of the parasite (Boots and Begon 1993; Box 4).

Direct, compelling evidence of fitness costs associated with resistance in natural populations is lacking. What is needed ideally is measurements of genotype by environment interactions for fitness-related traits in the wild, with exposure to parasites as the environmental factor. Just such an interaction is qualitatively described in a recent report of bumblebees (*Bombus terrestris*) parasitised by conopid flies (Müller and Schmidt-Hempel 1993). Parasitised bees stay in the field overnight rather than return to the hive. This has the effect of cooling the parasitoids which retards their developmental rate. Parasitised hosts therefore live longer, but at the cost of reduced help to the mother colony.

Measurements of the relative costs of different modes of resistance in the same host species would also be valuable; in vertebrate models, antigen- and germ-free environments, together with pharmacological agents and gene-knock out therapy provide the potential for disarming specific modes of resistance. These technological innovations offer the possibility of separating the cost of resistance from the cost of parasitism, but the extent to which they can produce data relevant to natural populations is unclear.

3.4 Virulence

What little theory and empiricism is available on the evolution of parasites themselves is, for the most part, concerned with the evolution of virulence. Extant theory (reviewed by Levin and Svanborg Edén 1990, Frank 1992)

Box 4. Costs of resistance to granulosis virus by Indian meal moths.

Six populations of the Indian meal moth *Plodia interpunctella* were maintained in the laboratory (Boots and Begon 1993). Three populations served as virus-free controls. The others were infected with self-perpetuating granulosis virus. The virus can be lethal, and is transmitted following host death. After two years, moths were cultured for two generations in the absence of the virus to rule out maternal affects and infection of assayed populations. The life histories of the selected and control populations were then compared. Resistance, as measured by LD_{50}'s, were almost twice as high in the populations maintained with the virus. This increased resistance was associated with longer larval development times and reduced egg viability which, in the absence of the pathogen, reduced fitness (measured as r) by 15% in the lines maintained with the virus. Maintaining the selected moths for two further generations in the absence of the virus reduced this difference to 8%.

Because mortality rates are dose-dependent, so too were the fitness benefits of resistance in the presence of the pathogen. Resistance had a selective advantage when virus inocula were small enough to induce mortality rates of less than 86% in the selected lines and 90.5% in the control lines. When doses were larger and mortality higher, the benefits of resistance were insufficient to outweigh the costs. Estimated mortality rates in the field are sufficiently low to allow the resistance detected in these selection experiments to spread, despite its associated cost.
Costs of resistance in Indian meal moths have also been suggested by a correlation between resistance to granulosis virus' and developmental times in six wild and two laboratory populations (Vail and Tebbets 1990).

focuses on the trade-off parasites face between destroying their food source (through host damage) and rapid growth and transmission, and now has some qualitative support (e.g. Ewald 1983, Bull *et al.* 1991, Herre 1993). But, with the exception of the myxoma virus in Australian rabbits, there have been no quantitative tests of theory. In that one case, theory has had limited quantitative success.

Anderson and May (1982), May and Anderson (1983) – see also Levin and Pimentel (1981) – used a simple differential equation model, a so-called 'SIR' model, to describe the dynamics of the interaction between rabbit and virus. The model can be used to derive an expression for the fitness of the pathogen, specifically the net reproductive rate or R_0 of the pathogen, in terms of the model parameters. This expression can in turn be used to predict the competitively superior strain of the pathogen. Anderson and May's key insight

is that the trade-off between death rate and recovery rate can be captured in the model by using existing data to empirically fit the recovery rate as a function of the death rate. This allows them to express the fitness of the pathogen in terms of the death rate of infected hosts; in other words, in terms of virulence. The resulting prediction is that pathogen fitness (transmission rate) is maximised for an intermediate level of virulence (R_0 is reduced by host immunity if pathogens are too benevolent, and by host death if they are too virulent). This matches the situation in Australia, but only qualitatively. In fact, the average level of virulence of myxoma strains in the field in Australia is substantially higher than Anderson and May's prediction.

Dwyer *et al.* (1990) attempted to improve Anderson and May's prediction by adding various kinds of realistic biological complexity. In particular, that changes in virulence lead directly to changes in the horizontal transmission rate of the virus, and that rabbit reproduction varies between seasons. In spite of this considerable increase in complexity (an increase in the number of parameters from 5 to 22), Dwyer *et al.*'s model performed only marginally better. Of course, many additional details might affect the coevolution of rabbit and virus, and it is difficult to know which would explain the discrepancy between theory and data. The issue proved controversial at the meeting and during the writing of this report. Some pointed out that sound quantitative estimates of relevant trade-off functions are difficult to obtain. Others pointed to the absence of explicit genetics in extant models and argued that incorporating quantitative genetics is the way forward. Many intuitively felt that models ignoring host resistance were likely to be at best incomplete. Still others believed, along with Anderson and May (1983 pp. 420–421), that taking into account details about the relationship between virulence and transmissibility (e.g. Massad 1987) is probably enough to reconcile theory and data, at least to accuracies consistent with common sense. The debate emphasised the issue of how close should we expect the fit of epidemiological models to be, and how might we distinguish empirically among different models producing equally good (or poor!) fits to the same data.

An alternative route to answering questions about the evolution of virulence is to work on a simpler and more experimentally tractable system. Insect baculoviruses, for example, are fatal and directly transmitted, they successfully evade host immune responses, and they are amenable to field experiments (Dwyer and Elkinton 1993). This reduced complexity relative to myxomatosis allows for easy estimation of R_0 in terms of virulence, transmissibility, and so forth. Encouragingly, quantitative predictions of the outcome of competition between different strains of a baculovirus of gypsy moths have been borne out by initial field competition experiments (Dwyer *et al.* unpublished).

Epidemiological approaches to the evolution of pathogen virulence thus

show the ability to accurately predict *a priori* the mean level of virulence of pathogens in the field. So far, however, no attempts have been made to explain the vast amount of variability in virulence that is seen amongst most pathogen populations, such as found in populations of *T. gondii* mentioned above, and in gerbil leishmaniasis (Dye and Davies 1990). Although it is possible that this variability is due strictly to ecological details, the more likely scenario is that the genetics of either host or pathogen are involved. Attempts to understand variability in pathogen virulence may thus lead to greater integration of ecology and genetics in the population biology of disease. Further provocative ideas about what current theory on the evolution of virulence does not even begin to explain are given in Levin and Svanbord Edén (1990). They suggest that virulence might be better viewed as an inadvertent consequence of within-host selection.

Before leaving the topic of virulence, we note that different authors use virulence in different ways. In some cases, disease severity in natural populations is at issue (e.g. Ewald 1983); in this sense, virulence is a property of the host-parasite interaction, and as much to do with host resistance as any parasite feature. Others take virulence to be a genetic trait of the pathogen itself (e.g. Levin and Svanbord Edén 1990). This latter sense is that used in the myxoma case, where changing virulence was assayed in standardised hosts (laboratory rabbits). In the plant literature, virulence is more often taken as the replication rate of the parasite within a host (e.g. Burdon 1987, Frank 1993). Whether these semantic differences obscure any conceptual difficulties is unclear. What is obvious, however, is that authors should explicitly define what they mean by virulence.

4 The future

We are only too well aware of what we did not cover during the meeting. For instance, nothing was said of the determinants and consequences of the genetic structure of parasite populations, of the congruence (or otherwise) between host and parasite phylogenies, or of the evolution of parasite life history strategies. Amongst the issues we did discuss, the ratio of ignorance to understanding was frightening enough. We do not believe that that was just a consequence of our expertise. Below, we attempt to list those unresolved issues which caught our interest during the meeting. However, we emphasise that this list is somewhat arbitrary and certainly incomplete; current knowledge is so limited, it is difficult to define even the central issues.

- How does incorporating genetics into population dynamical models affect the outcome? For example, what role might genetic variation play in stabilising host-parasite interactions?

- What epidemiological patterns are a consequence of genetic variation?

- Can we avoid over parameterisation of models incorporating genetical and population dynamical considerations? When is the genetics sufficiently simple to allow adding simple multi-clone dynamics into extant population dynamical models; when is the genetical and population dynamics sufficiently chaotic that the models can be treated as stochastic? Are explicit quantitative genetics necessary? Would they make things simpler?

- How should we incorporate immunological processes into models of host-parasite coevolution. Is there a conflict between somatic immune evolution within a host and conventional germline genetics? Perhaps in long lived hosts, the former is sufficiently described by extant models of the latter? Are there interesting interactions in shorter-lived hosts? To what extent do epigenetic processes like maternal transfer of acquired immunity impact on host-parasite coevolution?

- How do the mechanisms of host resistance affect the evolutionary and ecological dynamics of host and parasite? There are strong parallels with the study of aposematism, where the mechanism of predator learning has a major impact on the type of warning coloration that evolves (Guilford 1992).

- Under what circumstances are particular resistance mechanisms favoured by selection? For instance, when should plastic responses evolve? Is selection for improved immunocompetence actually for better nutritional acquisition? How does selection act on maternal tolerance or on concomitant immunity?

- How is population variance in immunocompetence partioned? What is the relative importance of differences in the ability to respond to parasite infection typically noted as species-specific, individual-specific and so on. If 'higher' vertebrates have the ability to respond to an infinite antigen diversity, why are there such differences?

- To what extent do we understand variation in virulence? Is the current emphasis on optimising parasite transmission sufficient?

- What are the consequences of considering evolutionary and population dynamic disequilibrium? Endemic persistence at population dynamic equilibrium, typically emphasised in evolutionary analyses, may be of less interest in a host-parasite context, where non-equilibrium states are clearly of great relevance (invasion of new pathogens, biological control, epidemics). Furthermore, the fitness of many traits in host-parasite

systems are typically both frequency and density-dependent. Yet most extant models of the evolution of virulence, for example, attempt to optimise parasite fitness assuming population dynamical stability. If such assumptions are inappropriate, how can we do away with them? One possibility is suggested by Nee and May (1993) in the broadly related context of intraspecific brood parasitism.

- Are epidemics the major source of selection on hosts, or are chronic infections more important? Does the nature of selection differ?

- Are there any generalities about the consequences of introducing new pathogens into a host population? Do we only hear about the disasters? Do the disasters only occur when there is a reservoir or continuous source of the pathogen?

- Are rare host and parasite genotypes at a selective advantage? This is particularly important in terms of the evolution of resistance to antiparasitic chemicals. The interplay between host-parasite population dynamics and genetics can be very complex. For example, Anderson *et al.* (1991) use simple models for the spread of anthelminthic resistance in nematode populations to demonstrate potentially intricate interactions between the dynamics of drug-resistant and susceptible parasite populations and the mating probability of rare genotypes.

- Is there heritable variation in the ability of both host and parasite to respectively resist and infect? Both of these issues lie at the core of notions about host-parasite coevolutionary cycles, yet there is precious little evidence for either from natural populations (see Lively and Apanius, this volume). Related to this, are parasite genotypes more successful at infecting the relatives of their hosts? There is some evidence of increasing mortality of measles for successive infections in the same human families in Senegal, although this has been attributed to more intense contract rates between relatives rather adaptation of the virus to genetically related people (Garenne and Aaby 1990).

- Are there any generalities about local coadaptation of hosts and parasites? More experiments involving sentinel organisms and reciprocal infections are needed. In such experiments, how can well adapted hosts be distinguished from poorly adapted parasites (and vice versa)?

- Sexually transmitted diseases are apparently ubiquitous in animals (Smith and Dobson 1992). Pollen and pollinator-transmitted diseases are also common in plants and have many features in common with venereal diseases in animals (Cooper *et al.* 1988, Antonovics 1992,

Thrall *et al.* 1993). How do STDs affect the evolution of host mating systems? For example, if sex is an anti-parasite adaptation how are STDs exploiting mating systems? What are the evolutionary consequences of STDs where transmission depends on the frequency of infectives rather than on host density, and thus requires different epidemiological framework?

Coda

We left the Newton meeting with the feeling that there was much to be done. The success of the NeoDarwinian Synthesis in evolutionary biology was in large part because it made sense of the enormous range of disparate facts collected by natural historians over several centuries. A similar (but infinitely more expensive) set of facts is beginning to be accumulated about host-parasite interactions by cellular and molecular parasitologists. Developing an evolutionary interpretation of these phenomena is an exciting challenge.

There was also a strong feeling that attention to genetics may lead to the emergence of richer and more valuable epidemiology. Quantitative analyses well grounded in theory are timely, but will not be easy, because of the additional complexity added by genetic parameterisation. But conceptual and technical advances place us in a position to escape from the inertia that has, in this context, swept genetics under the epidemiological rug.

Acknowledgements

We are grateful to Bryan Grenfell and Andy Dobson for organising the meeting; the Director, staff and benefactors of the Newton Institute for making us welcome and providing financial support; and M. Begon, R.M. May and S.A. Levin for comments on earlier drafts.

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