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Pathogens, Polymorphism, and the Evolution of Sex

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For short-lived pathogens, adaptation to one host genotype is negatively correlated with adaptation to others when host genotypes are sufficiently differentiated. This may provide an adaptive basis for sexual recombination, which lowers cross-genotypic correlations among offspring and other kin, and thereby interferes with pathogenic transmission, multiplication, and adaptation. Such pathogen–host interactions lead to generalized frequency-dependent selection for allozymic diversity. The ecological and life-historical correlates of parthenogenesis, inbreeding, chromosome number, and polymorphism are consistent with this hypothesis.

Introduction

The increasing theoretical precision, over the last two decades, of the conceptual revolution in evolutionary biology has isolated the question of the function of sexual reproduction as the one surviving issue which has resisted definitive assimilation into the individual selection paradigm (Maynard Smith, 1971). The disadvantages of sexual reproduction, including the costs of meiosis, recombination, and mating are large, while the advantages remain obscure (Maynard Smith, 1978). The most effective advocate of the individual selection viewpoint, G. C. Williams, has advanced a set of models showing sufficient advantage to sexual reproduction only under certain combinations of ecological and life historical conditions (Williams, 1975). The relevance of some of these models to natural circumstances has been disputed (Maynard Smith, 1978), but regardless of their validity, the models are not sufficiently universal to account for the present distribution of sexually reproducing species. This forced Williams to conclude that the costs of sex heavily outweighed the benefits among low fecundity taxa, such as birds, mammals, reptiles, and many insects.

At approximately the same time that sexual reproduction was emerging as a major evolutionary anomaly, electrophoresis and the selective assay of enzymes was applied to population genetics, uncovering a surprising and theoretically unexpected degree of protein polymorphism (Lewontin & Hubby, 1966). The nature and significance of this genetic variation is still a matter of varied interpretation (Lewontin, 1974; Ayala, 1976; Nevo,

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1978). The analysis presented here suggests one way in which sexual reproduction and a major proportion of the protein polymorphism may be related phenomena, the result of selection acting at the individual and kin level in response to rapidly evolving pathogens.

Multicellular organisms are continuously exposed to the micro-organisms present in their environment, and form potentially colonizable habitats. For the vast majority of micro-organisms, conditions on a specific host are adverse for survival and reproduction, but for some, a given individual provides a suitable habitat for colonization and multiplication. A subset of the successful colonizers, the pathogens, have a negative effect on the fitness of the host, and no known multicellular organism is without such colonizers. For a pathogen to have a negative effect on its host it must be able to reproduce inside the host, and therefore the suitability of the host for a specific pathogen will (in part) determine the magnitude of the negative impact of the pathogen on the host. The measure of host suitability that will be used in this analysis is the average generation time of the colonizer when successively reproducing inside the host. If the micro-environment that a specific host constitutes is favorable, pathogenic reproduction will be rapid, generation time will be short, and eventual pathogenic population size may be large. If a specific host is less suitable, the pathogen will require a longer time to reproduce, and may never attain maximum population size. A pathogen which cannot reproduce at all inside a given host can be said to have an infinite generation time.

The number of generations and total resultant population of the invading pathogen may be immense, with the ratio of generation times of the host to the pathogen occasionally being in the tens of millions. As a result, unless at the time of infection the pathogen is already maximally adapted to the host's specific genotype, the pathogen will undergo significant evolution during its colonization of a single host, adapting it more closely to the particular characteristics of that micro-environment. The pathogens will then be more suited to colonizing habitats more closely resembling the micro-environment of the previous host. The major factor controlling the similarity of hosts is the correlation between their genotypes. In short, if the pathogens are well-adapted to the previous host, *the new hosts most at risk will be the previous host's close kin and offspring.* Sexual recombination significantly lowers the correlation between the genotypes of kin, thereby decreasing the probability of infection, lengthening the pathogen's generation time and *slowing its rate of adaptation.* The decrease in cross-genotype correlation caused by sexual reproduction is large over even one generation, and becomes very powerful over multiple generations. For example, a random mating increases within progeny variance to one half

of the variance of the total population. (Cross-genotypic correlation is defined as the correlation between the genotypes (by state) of two individuals taken over all loci.)† The magnitude of this effect depends on the relative generation times of host and pathogen, the sensitivity of the pathogen to host genotype, and the maximum attainable intra-host population size of the pathogen.‡ (Maximum intra-host population size attained will be a function of many factors, of which the most significant are the size of the host and the relative generation times of host and parasite. Host size and relative generation time, however, are associated closely enough that for present purposes, the single measure of relative generation time is sufficient.) The greater the ratio of relative generation times is, the more evolutionary change the pathogen undergoes and the greater will be the difference between the genotypes of the pathogens infecting the host and the pathogens the host infects others with. By the same token, the smaller the ratio of generation times is, the less evolution will take place for the

† The importance of ρ is as a measure of the genetic structuring of the phenotypic similarity (from the parasite's point of view) between the parasite's host and the successor host. This is why, for ρ, unlike many other measures of relatedness, identity by state rather than identity by descent is the relevant procedure. Diploidy is handled by taking the alleles at each locus in a non-ordered way. The best measure would be limited to those genes which potentially interact with parasites' genotypes, but this is difficult to determine, and is unlikely to be very different from ρ. Across a substantial number of generations, the total number of species that parasitize a host species may be quite large, and therefore, in all probability, the genes that the aggregate of parasitic species are sensitive to will be distributed across the host species genome. Even if there were some unknown tendency to concentrate them, selection would oppose it.

‡ More precisely, the amount of evolutionary change a pathogen is capable of undergoing in a single host is a function of both generation time and the maximum population size the pathogen achieves. Each new individual parasite is another opportunity for mutation and selection. Maximum population size is related to the size of the host, its lifespan, and its metabolism and defenses. In the simple case of unopposed exponential population growth, ultimate parasite population size is a direct function of generation time. In the case of vertebrate immunological defenses, there is often a race between pathogenic reproduction and the initially lagging immunological system, also creating a relationship between pathogenic generation time and maximum population size. For these reasons, relative generation time and maximum intra-host population size are closely enough related that generation time can be used.

An interesting feature of this relationship is the possibility of feedback between the rate of the pathogen's evolutionary change and the pathogen's intra-host generation time and consequent population size (over much of the range of intra-host population size): the more poorly adapted a pathogen is, the smaller its intra-host population is, and the less evolutionary change it can undergo in the coevolutionary race. If the pathogen is less well adapted to the host lineage, and is kept at extremely small population sizes, then it may be kept from relatively increasing its adaptation to the host. Also, with many infectious diseases in vertebrates, the initial dose received must overcome a threshold effect in the immunological system. If pathogen populations are kept low, there is less likelihood that dosages sufficient to overcome the immunological system will be present. The implication of such a feedback relationship is that incrementally increasing recombination may have a disproportionately negative effect on parasite fitness.

pathogen relative to the host, and the smaller the effect. This is the reason why relative generation time has been selected as the index of host suitability most appropriate for the analysis that follows. If the ratio is large enough, the fitness of the host's genotype may become zero within a single generation.

The central assumption in this analysis is that the success of pathogens depend on the interaction of the genotypes of the specific parasite/host pairs, and that this be a widespread feature of such interactions. This assumption appears to be plausible, based on both the available evidence (for reviews of such interactions, see Clarke, 1979; Day, 1974) and more general considerations. No known pathogen is capable of infecting all or even a very large subset of existing species, and most appear to be basically species-specific (Marchalonis, 1977). Since it is the genetic differences between species which meaningfully differentiate them, relative susceptibility to a specific pathogen must have some genetic component. That, taken together with the Darwinian principle that within species variation is what produces between species variation, indicates that it is likely that generally, parasite susceptibility is the result of the interaction of host and parasite genotype.

There are many possible ways to formalize these relationships. Fortunately, this approach is robust to a large number of variations in premises and formulations, showing the necessary more-than-twofold advantage to sex within a broad range of biologically plausible parameters. The model presented is the simplest one which retains all the properties essential to the hypothesis and which is usefully testable given the presently available data. The difference in fitness between competing sexual and asexual forms is attributable to the eventual larger pathogenic load borne by the parthenogenic form, and within certain parameters, the fitness of the parthenogenic form will decrease to zero. This pathogenic load will be a function of the sequence of cross-genotypic correlations (ρ) between successive hosts.† The greater the correlations, the shorter the pathogen's

† The longer the parasite's generation time is relative to the host's, the more important the *sequence* of previous hosts becomes. If the parasite's generation time is short enough relative to the host, the heritability of host resistance will be negative. When the parasite's generation time becomes long enough (or the host's, short enough), the heritability of fitness will be positive for one or more generations, only episodically becoming negative. As a result, the amount of recombination selected for will be determined by the constellation of generation time profiles of the various parasites the host species is subject to. Also, the profile of ρ's a pathogen encounters is dependent on its particular patterns of transmission and consequent actual sequence of hosts, so maximum ρ's are far more important than average ρ's among potential hosts. Offspring in a species with low chromosome numbers have the same average relatedness to each other as do offspring in species with high chromosome numbers, but within progeny genotypic variance is smaller.

generation time, g, will be, and the greater the ultimate load. The generation time is scaled with respect to the minimum generation time, κ, of the pathogen that would occur if every successive host were genetically identical to its predecessor. The total population of pathogens reached in a host will be $e^{h/g}$ (or a lower limit†) where h is the generation time of the host and g is the generation time of the pathogen. If g is inversely proportional‡ to ρ, the genotypic correlation between successive hosts, then $g = \kappa/\rho$, and $e^{\rho(h)/\kappa}$ is the total population of a strain of pathogen in the host. Because parthenogenic reproduction maintains cross-locus genetic associations, the genotypic correlations of successive hosts will be higher for parthenogens, so the difference in pathogenic loads between sexual and asexual competitors will be

$$L_a - L_s = \sum_{i=1}^{n} \lambda_i (e^{\tilde{\rho}_i(h)/\kappa_i} - e^{\hat{\rho}_i(h)/\kappa_i}) \tag{1}$$

summed for each specific pathogen where L_a is the pathogenic load on asexual hosts, L_s is the load on sexual hosts, n is the number of pathogens, λ_i is the fitness decrement suffered by the host for each additional pathogenic individual of strain i, $\tilde{\rho}_i$ and $\hat{\rho}_i$ are the mean inter-host genotypic correlations pathogen i encounters among asexual and sexual hosts, respectively, and κ_i is as defined above. If, in the absence of pathogens the fitness of an asexual reproducer is considered to be twice that of a sexually reproducing individual (i.e. $W_a/2 = W_s$), then for sexual reproduction to be adaptive,

$$W_a - L_a < W_s - L_s \tag{2}$$

or

$$L_a - L_s > W_a/2. \tag{3}$$

† Population growth is, of course, generally sigmoidal rather than exponential, and other logistic equations can be substituted without qualitative change to the results. If this is done, maximum pathogenic population size should also be included as a metric of host suitability and hence as a function of ρ. In addition, host fitness reduction should not only be a function of eventual parasitic population size, but also of the rate at which maximum load is reached. Also, the real relationship between the population size of parasites and the fitness decrement for the host is no doubt stronger than is here assumed: the fitness loss per additional parasite will be disproportionately greater the larger the intra-host population size. This would act to make the benefit of recombination greater.

‡ The relationship between ρ and the generation time of the pathogen is a question of central importance. What has been used for heuristic purposes is a simple relationship, with generation time being inversely proportional to ρ. In actuality, the particular relationship of g to ρ will be dependent on the specific pathogen, but all that is essential for the model to be applicable is that g should increase as ρ decreases. The effects of genetic uniformity on epidemics (Day, 1974) indicates that, for most pathogen–host pairs, this relationship is likely to hold.

As the lifespan of the host increases relative to the pathogen, it is easier to find biologically plausible parameters yielding advantage to sexual over asexual forms.

Protein Polymorphism

The discovery of vast reservoirs of enzymatic variability precipitated a debate between those who argued that most alleles were selectively neutral, and those who argued that they were maintained by balancing selection (King & Jukes, 1969; Kimura & Ohta, 1971; Ayala, 1976; Johnson, 1974). In this debate, it has been customary to differentiate the chemical structure of a protein from its function, which may manifest itself as some phenotypic trait coherently related to some feature of the external environment. Thus, neutralists argued that structurally different proteins (produced by different isoalleles) were usually functionally equivalent, and hence selectively neutral. It bears pointing out, however, that from the point of view of invading pathogens, it is the structure of the proteins that creates the biochemical micro-environment that the micro-organism inhabits. The pathogen uses for its reproductive activity the enzymes, substrates, and biochemical pathways it is exposed to, rather than necessarily the ultimate functional product of such pathways. Moreover, a wide variety of studies of electrophoretically detected enzyme variants uniformly reported significant differences in kinetic behavior. Differences are observed in stability, in reaction rate, in binding affinity of enzyme for substrate or cofactor, and in the sensitivity of such binding to temperature. Also, evidence indicates that the overwhelming majority of allozymes are conformationally distinct (Johnson, 1975, 1976). Regardless of whether such differences alter the functional products of different processes (the metabolic "phenotype"), they may differentiate the cellular and extracellular environments pathogens encounter. For this reason, individuals with functionally equivalent but structurally different proteins may be differentiated habitats from the point of view of the microbial colonizer. In such cases, a pathogenic strain adapted to one set of isoalleles will be maladapted to others.

Haldane, in his prescient 1949 paper, was the first to point out the potential significance of disease in generating and maintaining genetic variability. He noted that selection on individual alleles would be frequency-dependent, and because the majority of parasites would be more adapted to the commonest alleles, the rare forms would enjoy a fitness advantage. Damian (1964, 1979) has pointed out the role of antigen mimicry in maintaining certain specific types of frequency-dependent polymorphism. Recently, Clarke (1976, 1979) has reviewed both the logic and extensive

evidence for the regulation of resistance polymorphisms by parasites on a gene-for-gene basis, and has argued that such selection pressures may account for a major fraction of the existing polymorphism.

The existence of multiple alleles at a large proportion of loci in a population considerably complexifies the series of environments faced by pathogens. This is particularly true of sexually reproducing species. Viruses, bacteria, and (to a lesser extent) fungi and protozoans have far less DNA than their host species, meaning that at least for some subset of the pathogenic genome, *specific microbial genes will be adapted to the simultaneous action of multiple host genes.* The pathogen "experiences" the host's phenotype as a unit, not decomposed into single features with single one-to-one correspondences with the parasite's genes. Even relatively simple metabolic processes in the host can be under the simultaneous regulation of an enormous number of different loci. While some cases of gene-for-gene host–pathogen interactions have been found, few if any have been unambiguously identified in nature (Day, 1974), and it is difficult to see how genetic interactions could be limited to such locus-for-locus interactions. Selection on the parasite does not distinguish what parts of the host phenotype are permanently "linked" (most characteristically by being caused by a single locus) from those that are temporarily associated, this being unpredictable from the point of view of the pathogen.† The pathogen cannot restrict the adaptation of each of its loci simply to those characters of the host phenotype which are determined by a single gene. *Sexual reproduction in the host species rapidly breaks up these associated gene complexes, effectively reducing the adaptive match between pathogenic genotype and successor host genotype.* If these hypothesized selection pressures exist, they will tend to regulate everything which maintains cross-locus associations (such as inbreeding, kin aggregations, linkage, etc.) in the sequence of hosts a pathogenic strain encounters.

Variation at the individual locus is a special and possibly weaker case of what may prove to be a more powerful phenomenon: the variation introduced into cross-locus associations. Polymorphism is the raw material out of which new combinations and associations are constructed and

† Over the long run, some components of selection on the parasite will tend to link the parasite's host-sensitive characteristics in concordance with how the host species linked its parasite-influencing phenotypic characters. Since any higher order genetic associations must necessarily be less probable than the component polymorphisms that make them up, a parasite which was adapted on a gene-for-gene or linked group for linked group basis would have an advantage, when considered over the lifespans of many hosts. As a result, such selection for linkage will be far slower than intra-host selection. Shorter run selection within the lifespan of the host would interfere with this process, selecting for any parasitic gene which shortened generation time, regardless of whether its efficacy was dependent on unlinked aspects of the host phenotype.

subsequently broken down, and the primary advantage of sex may be derived from the continual destruction of such cross-locus associations. As a result, the more alleles that exist at more loci, the lower the mean cross-host cross-genotypic correlation (ρ) and the more frequently cross-locus associations will be broken down. A number of factors, including selection, lack of dispersal, drift, inbreeding, kinship, and vertical transmission of pathogens, are always increasing inter-host genotypic correlations, and even with sexual reproduction the absence of a sufficient degree of polymorphism would not sufficiently differentiate individuals.

Even with gene-for-gene relations, most pathogens will be adapted to structurally common proteins, making individuals with rare alleles less susceptible to parasitism. With higher level interactions, the relative frequency of formation of a cross-locus association will create a similar process of frequency-dependent selection promoting polymorphism. If parasitism is a signficant selection pressure, such frequency-dependent selection will be extremely widespread across loci, with incremental advantages accruing to each additional polymorphic locus which varies the host phenotype for a pathogen. Such a process will lead to the accumulation of considerable allozymic diversity in populations. Of course, any specific pathogen may be inhibited by only a small subset of the diversity present, but the net effect of many pathogens over multiple generations should be to make the structure of such diversity far greater than predicted for stochastic processes acting on selectively netural alleles. Evidence reviewed below suggests that it is.

Predictions and Evidence

According to degree of recombination, reproductive strategies can be arrayed along a continuum from apomictic parthenogenesis to automixis and selfing, through degrees of inbreeding, to outbreeding, to outbreeding with frequent mate changes, to dissassortative mating. If the above outlined argument is true, the distribution of reproductive strategies should be associated with generation time, with extremely short-lived organisms pursuing low recombination per generation strategies, while long-lived organisms would be pursuing high recombination per generation time strategies. The observed taxonomic distribution of sexual reproduction is consistent with expectation. The proportion of sexual reproduction to asexual reproduction increases with generation time across taxa (for review see Ghiselin, 1974), from the overwhelmingly asexual Monera to the obligately sexual long-lived vertebrates and invertebrates. The universally or almost universally sexual low fecundity taxa which stand out as anomalous in other models (Williams, 1975) match expectation in the

pathogenic model. The degree of inbreeding is a measure of the selection for recombination, and it is notable that not only are these groups overwhelmingly sexual, but the longer-lived of them are outbreeders as well (Bischof, 1975). Among ciliate protozoans, Sonneborn (1957) found that the reproductive characteristics correlated with generation time. Inbreeders have short generation times while outbreeders are typified by long periods of immaturity and maturity, which may extend over months or years. Outbreeders have a slow rate of fission and may have multiple mating types. In plants, dioecy is generally agreed to be an adaptation to insure outcrossing, and it is striking that dioecy is rare among herbs, more common in shrubs, and most common in trees (Maynard Smith, 1978 p. 136).

The ecology of microbial colonization and pathogenic transmission will also be a major regulator of selection by pathogens for recombination. Those species whose mode of subsistence exposes them to exceptionally high concentrations of pathogens (detritus eaters, pond surface dwellers, and so on) will be selected to manifest higher degrees of recombination. Bacterial, protozoan, and fungal growth and contagion are facilitated (within limits) by increased temperature and moisture. Bacterial populations, for example, can be increased several thousandfold on the skin by increasing moisture available (Marples, 1965). Contagion is also facilitated by increased host density. Therefore, selection for recombination should show the following.

(1) A *generation time effect*, as described above.

(2) A *latitudinal effect*, with increasing rates of recombination from the poles to the tropics.

(3) A *humidity/moisture effect* with xeric environments showing less recombination than mesic ones.

(4) A *density effect*, with recombination increasing as local host density increases.

(5) An *altitudinal effect*, with recombination decreasing as altitude increases.

(6) A *kinship effect*, with recombination increasing where there is parental care or extended kinship association.

(7) A *sessility effect*: because of increased viscosity and the inability of sessile organisms to escape increasingly adapted concentrations of pathogens, recombination should increase with sessility. On the other hand, pre- and post-zygotic dispersal should reduce mean cross-genotypic correlations pathogens encounter, as a function of the distance of dispersal.

(8) A *restricted-habitat effect*: since islands and others restricted habitats maintain lower pathogenic loads, selection for recombination will be reduced (Glesener & Tilman, 1978).

(9) A *continuous range–population size effect*: each individual acts as a possible point of entry and a reservoir for pathogens, and the larger the population size and the more continuous the range, the greater the parasitic load will be. Also, the more different environments a species extends through, the more different reservoirs and varieties of pathogens the species is exposed to, which can then be transmitted to conspecifics beyond the original range of the parasite.

(10) Selection for recombination should be paralleled by frequency-dependent selection for increased polymorphism, so the above listed correlates of increased pathogenic load should also be associated with higher levels of polymorphism and concomitant heterozygosity. Similarly, where applicable, the correlates of increased pathogenic load should be associated with increased species diversity, since that also reduces (from the point of view of a pathogen) cross-genotypic correlates.

(11) Levels of polymorphism should be higher for genes coding for tissues more exposed to infection, more involved in defense, or controlling physiological variables with the greatest impact on the environment pathogens encounter. For example, some loci in the human HLA complex have more than 20 alleles (Bodmer & Bodmer, 1978).

If the pathogenic model is correct, there should be intense selection modifying breeding systems and mating behavior. For a more precise testing of these hypotheses, a taxonomy of mating systems appropriate to this model needs to be developed, indexing mating systems and associated mechanisms by their impact on the degree of recombination and genetic variability in the offspring produced. Heterozygosity per locus per individual is clearly a key variable in such a taxonomy. The amount of inbreeding and the features of the mating system which regulate genetic distance between mates (e.g. self-sterility, negative imprinting, dioecy, distance of dispersal, wind pollination vs. insect pollination, etc.) are another relatively well-understood dimension of such a taxonomy. Fecundity also influences offspring variability. Mate number (per offspring produced) is a more neglected dimension governing a parent's offspring variability and the variability in the local offspring generation, and can be used to array mating systems along a spectrum. An individual who increases mate number is increasing offspring variability for itself at the expense of decreased variability in the local offspring generation for its mates (except in the unlikely case where each new mate increases its own mate number exactly in proportion). The offspring of multiple mates will share genes through a single parent. For example, extreme and enduring polygyny offers minimum variance in the offspring generation to females. The negative consequences of this for females may lead to some tendency for females to avoid mating

with males whom other females disproportionately mate with, in opposition to Fisher's (1930) principle of run-away selection, and in opposition to the advantage of preferentially selecting males who have otherwise superior genotypes. However, when the pathogen profile allows a temporary positive heritability of resistance, females (or males) may choose mates on the basis of their assessment of such resistance, leading to at least some clustering of mate choice. Among those systems with low variance in reproductive success, annual monogamy offers more offspring variability than lifelong monogamy, while (low RS variance) promiscuity offers the most of all. Multiple inseminations, such as occur among some eusocial insect species and in many primates, may prove to be an important variable regulating offspring variance.

The ecological distribution of breeding systems for plants and animals tends to be compatible with many of these predictions. In plants, parthenogenesis and selfing are rare in tropical environments, while dioecy is more frequent (Bawa & Opler, 1975; Levin 1975). For example, in *Taraxacum* (the dandelion), the apomictic species are associated with arctic, alpine, and cool temperate habitats, while the sexual species tend to be distributed at lower latitudes (Richards, 1973). Also, their system of dispersal pre-adapts them for parthenogenesis by allowing escape from localized adapting pathogens. In reviewing parthenogenesis in terrestrial animals, Glesener & Tilman (1978) following up the work of Suomalainen (1950) found that, in comparison to the nearest sexual species, parthenogens occur in drier and higher conditions, at higher latitudes, and on island or island-like habitats. (They themselves attribute the distribution to biologically induced environmental uncertainty created by sexuality, predation, competition, parasitism, and other components influencing interspecific interactions.) Within species, where evidence is available, the picture that emerges is similar. For example, in the millipede *Polyxenus lagurus*, parthenogens are rare in France, but steadily increase with latitude until in Finland, the frequency is 100% (Palmen, 1949).

Hamrick, Linhart & Mitton (1979) found significant correlations between a number of different aspects of the breeding system and generation time using a sample of 100 plant species. The degree of outcrossing is significantly correlated with longer generation time. Similarly, pollination mechanisms, arrayed according to the degree of recombination from selfing to animal to wind pollination, is significantly positively correlated with generation time. Moreover, seed dispersal distance is strongly positively associated with generation time, as is fecundity.

Pathogens will be adapted to the genotypes and associated gene complexes of the local host population in proportion to their frequency. Hence,

immigrants and other individuals with low average genotypic correlations with the local population will have offspring with higher than average fitness, other things being equal. Individuals (particularly females) would be selected to preferentially mate with rarer genotypes. This "rare male" effect has been reported in seven *Drosophila* species (virtually every species tested), in *Tribolium* beetles, birds, teleosts, and apparently mammals (for reviews, see Ayala & Campbell, 1974; Farr, 1977).

Individual genotypic differences are maximized when alleles assort independently, so selection to increase recombination should increase chromosome number. Due to increased contagion, high chromosome numbers are expected to be associated with high host densities. In insects, the highest population densities are reached in colonies, and, as expected, eusocial insects have elevated chromosome numbers compared to their non-social relatives and ancestors (Sherman, 1979; Seger, 1980). Similarly, non-eusocial species manifesting larval aggregations and sibling asociations have higher chromosome numbers than do non-eusocial species whose larvae are non-gregarious (Sherman, 1979). Similar results have been obtained in birds and ungulates, indicating associations between size of conspecific associations and chromosome number (Tooby, in preparation). In plants, recombination restricting features such as low chromosome numbers and localized chiasmata are rarer in tropical than in temperate habitats (Levin, 1975).

Selection for greater recombination will also intensify frequency-dependent selection for increased polymorphism, and in fact the same trends found for recombination mechanisms appear to typify the data on polymorphism. Heterozygosity per locus per individual (H) will be a somewhat more relevant measure than polymorphic loci per population (P) since it gives the stronger indication of how likely a given event of sexual recombination is to disassociate one allele at one locus with another allele at another locus. 80% of the intersample variation in heterozygosity for 23 mainland populations of *Peromyscus polionotus* is accounted for by latitude (in the predicted direction) (Selander *et al.*, 1971). Across species, the same pole to tropics trend in variability has been reported in *Drosophila*, benthic marine invertebrates, fish, and pelagic invertebrates (Valentine, 1976; Somero & Soule, 1974; Valentine & Ayala, 1976). A similar picture emerged from Nevo's (1978) more extensive review of the data. Tropical species were found to be significantly more heterozygous than others. Only for *Drosophila* are there presently enough data to test the latitudinal hypothesis more narrowly at the genus level. Using Nevo's data to test whether tropical populations contain more heterozygosity than temperate

ones do, a significant association ($p < 0{\cdot}004$) in the expected direction† is found. Selander & Kaufman (1973), in summarizing the electrophoretic data on animals, found sessility to be associated with higher levels of polymorphism. There are fewer data on the relationship between moisture and heterozygosity, but the availabile facts do not appear to be contrary to expectation. For example, in *Avena barbata* there is a cline from mesic to xeric conditions in degree of variability, with xeric samples nearly monomorphic for loci tested (Clegg & Allard, 1972; Hamrick & Allard, 1972). While data are at present too few to permit statistical analysis, the desert *Drosophila* populations listed in Nevo (1978) all have heterozygosities sizably below the genus mean. At moisture extremes, Nevo found aquatic vertebrates to be significantly more heterozygous than non-aquatic vertebrates. More generally, Hamrick *et al.* (1979), using a sample of 100 plant species, reported a significant correlation between moisture in habitat and heterozygosity in the expected direction. They also found that longer generation time was significantly correlated with increased heterozygosity.

If enzymatic variation were selectively neutral, then the level of polymorphism should be a function of the size of the breeding population and the mutation rate (Kimura & Ohta, 1971). However, evidence on the frequency and patterns of protein polymorphism does not tend to correspond to the predictions of neutralist theory (Clarke, 1979; Nevo, 1978). Instead, the discrepancies observed are what would be expected if pathogens were a major selective force. Generalized frequency-dependent selection should produce allelic frequencies that are more even than those that would be produced if stochastic processes were dominant. That allelic frequencies are, in fact, too even has been shown by Johnson & Feldman (1973) for *Drosophila*, and by Haigh & Maynard Smith (1972) for human hemoglobin variants. Furthermore, frequency-dependent selection would produce a different population size–polymorphism relationship than would neutral stochastic processes. Such selection for recombination would maintain higher than chance diversity among small populations, but would show only a slowly (rather than sharply) increasing relationship between population size and heterozygosity over the upper range of N. This distribution is, in fact, what is found (Lewontin, 1974 pp. 208–212; Soule, 1976), and could only be accounted for by stochastic processes if humans, mice,

† Populations were divided on the basis of whether they were either above or below genus mean heterozygosity, and by matching this against Nevo's categorization of those populations as either tropical or temperate, one finds a significant association ($p < 0{\cdot}004$) in the expected direction using Fisher's Exact Test.

Drosophila, horseshoe crabs, and a large variety of other species all had populations within a single order of magnitude (Lewontin, 1974).

Damian (1964, 1979) has explored the importance of antigen sharing in maintaining certain types of protein polymorphism. For immunological systems to be able to attack invading pathogens, they must be able to recognize them as distinct from body tissues. Pathogens which acquire or evolve antigens identical to (or indistinguishable from) body tissues will not be recognizable by the host. As a result, the more different alleles present at a locus specifying a type of antigen (e.g. bloodtype), the more frequently an invading pathogen will be identified as distinct from the host's antigens. For example, the human ABO polymorphism has been found in a number of primate species, indicating that it is probably quite ancient. Brues (1954) pointed out that the relatively narrow distribution of ABO blood-group frequencies would be hard to explain in the absence of balancing selection. Yet, due to maternal–fetal incompatibility (Cavalli-Sforza & Bodmer, 1971), there is significant selection against heterozygotes which, if uncounteracted, would have led to the elimination of the polymorphism. Interestingly, however, cross-reacting substances resembling the ABO antigens are found in numerous pathogens, including *Shigella*, *Salmonella*, and *E. coli*. Such substances are expected to influence the course of an infection. A pathogen carrying an antigen cross-reacting with A on its cell surface would have greater success infecting a type-A individual, because such a host would not be able to respond by the production of anti-A (Cavalli-Sforza & Bodmer, 1971, pp. 209–212). Such host–pathogen interactions would cause the ABO polymorphism to behave in a frequency-dependent fashion, despite the reported heterozygote disadvantage.

The most persuasive argument that sexual reproduction is not maintained by group selection is G. C. Williams' balance argument (Williams, 1975). Facultative parthenogens which cycle between asexual and sexual reproduction, such as rotifers, cladoceran crustaceans, and aphids, should evolve quickly toward obligate parthenogenesis if there were not some counterbalancing short-run advantage to sexuality. Using the ecological correlates of the timing of sexual cycles, Williams proposed that sex is the parental adaptation to changed conditions for offspring, and suggested that the sexual generations should occur when environmental differences are largest between the parental and offspring generations. However, as Birky and Gilbert point out in their review of rotifer reproduction, "the transition from asexual to sexual reproduction is not simply attributable to change in the environment. . . . Specific controlling factors can be identified" (Birky & Gilbert, 1971). These factors, for the most part, appear to be the ecological correlates of pathogenic propagation and adaptation.

The pathogenic hypothesis, applied to cyclical parthenogens, relates these variables somewhat differently. Microbial growth tends to be sigmoidal, with long periods of low population with subsequent precipitous increase. (The process of adaptation should make this curve flatter in the initial stages and steeper in the later stages.) If such microbial growth and adaptation spikes are substantially shorter than the generation time of the host, then heritability of fitness will be negative and sexual reproduction should occur every host generation. When the host generation time drops substantially below the length of this pathogenic adaptation process, the host can afford asexual generations as well, with the value of a sexual generation increasing with the passage of asexual generations. The ratio of sexual to asexual generations should tend to increase with host generation time, and the periods of sexual reproduction should tend to be separated from each other. Asexual generations should take place when the host can reproduce the most quickly, while the sexual generations should take place when reproduction slows. Perhaps most importantly, however, asexual generations should take place when host density is lowest, while sexuality should appear when host densities are highest. Also, due to increasing microbial adaptation, sexuality should become more favored as the time from the founding of the host population progresses and habitat occupation lengthens.

The ecological factors which appear to govern the transition from asexual to sexual reproduction seem more consistent with the pathogenic hypothesis than with the environmental uncertainty hypothesis, at least in those taxa Williams (1975) used as model cases. Where evidence is available, density appears to be the most significant factor, at least in rotifers and cladoceran crustaceans. Field studies of rotifers in a number of genera have shown that they are mictic solely or predominantly during density maxima, and laboratory work has confirmed this finding, demonstrating that the proportion of mictic females increases with density (Carlin, 1943; Birky & Gilbert, 1971). A similar picture applies to cladoceran crustaceans, with, for example, sexual reproduction always accompanying population peaks among *Daphnia magnia* (Hebert, 1974). Similarly, bacteria recombine primarily at high densities, and are evidently incapable of it in the early stages of a colonial growth cycle (Fisher, 1971).

Generalizations about the *Aphididae*, given their enormous diversity, need to be cautiously made, yet here too the evidence seems more consistent with the pathogenic rather than the environmental uncertainty hypothesis. The following facts are taken mostly from the reviews by Hille Ris Lambers (1966) and Kennedy & Stroyan (1959). There appears to be no clear and close correspondence between uncertainty of offsprings' habitat and sex,

except to the extent that one season differs from the next and the onset of winter initiates the production of hibernating eggs. If environmental uncertainty were the stimulus for sex, then alate dispersal to other habitats would be tied to sexual forms. However, almost all oviparous females are apterous, and so usually are the sexually produced fundatrices. Alates are generally parthenogens, and are produced primarily as the result of high local density, which has its effect independently of feeding competition or resource exhaustion. Other factors, such as humidity, withering of the host plant, prolonged contact between the mother and larvae, and the advanced age of the clone (i.e. the high number of generations since the last sexual generation) increase the number of alates produced. Many of these factors are correlates of pathogenic adaptation and propagation, to which dispersal is one effective response. Similar factors govern the production of sexuals by both apterae and alatae. Declining temperature and photoperiod signal the slowing of reproduction, and these factors together with high density and increasing time since the last sexual generation stimulate the production of sexuals.

Finally, the divergent reproductive patterns of organellular genes, such as mitochrondrial DNA, and nuclear genes provide additional support for the pathogenic hypothesis. Regardless of the phylogenetic origin of mitochondria, they can be viewed as obligate endosymbionts capable of significant evolution and diversification over the cell cycles of their eukaryote "host" (Grun, 1976; Margulis, 1970). In this, they differ markedly from the nuclear DNA which is exactly conserved over mitotic cycles. In effect, the generation time for mitochondria is substantially shorter than that for nuclear DNA, meaning that to be consistent with the pathogenic hypothesis, mitochondria should undergo far less recombination. This is in fact the case, with recombination rates very low and the predominant mode of reproduction being asexual fission. This low rate does not appear to be the result of phylogenetic constraint, since there is evidence to indicate that recombination could be substantially increased if there were selection for it (Birky, 1978; Cosmides & Tooby, 1981).

The facts presented are far from uniquely explained by the pathogenic hypothesis, and no doubt many counterexamples could be found. Individually, most of these results have had alternative hypotheses advanced to account for them (e.g. heterozygote advantage, environmental grain, species age, stability of population size, spatial or temporal environmental uncertainty, geographic range, etc.). The purpose of this brief survey is to indicate that there are many lines of potential validation, and that the major features of the relevant bodies of evidence are not inconsistent with the pathogenic hypothesis.

Additional Host Strategies

The existence of extremely short-lived rapidly adapting pathogens has brought forth many forms of defense by the longer-lived. Sexual recombination, by differentiating successive environments the pathogen must adapt to, exploits the short generation time and rapid adaptability of pathogens. Other morphological and life history characteristics may perform the same function by exploiting the same principle.

(1) *Tissue differentiation*: cellular differentiation by the activation of different gene complexes in different tissues increases the environmental heterogeneity the pathogen faces among genetically identical cells. Mosaicism has the same effect.

(2) *Facultative phenotypic variation*: identical genotypes may express different phenotypes, as the result of developmental noise or plasticity, and this may interfere with parasitism in much the same way as tissue differentiation does. Phenotypic differentiation caused by genotypes that are sensitive to variation in micro-environmental characteristics should be selected for even when the changes are otherwise selectively neutral with respect to such environmental variation. Also, such selection may act to increase functional facultative variation. For example, morphological differentiation between castes in the eusocial insects may, as a secondary function, act as an impediment to parasitism. More directly, the immunological system is capable of generating enormous internal diversity within a single host over very short timespans.

(3) *Development and metamorphosis*: long-lived eukaryotes can take advantage of their larger genomes by activating different sets of genes at different points in the life cycle.

(4) *Host lifespan*: selection should also act to reduce the host's lifespan relative to the pathogen's generation time. The longer a host lives, the more cost (in terms of pathogenic evolution and total pathogenic numbers) it is inflicting on its kin and offspring. Selection for accelerated mortality should be particulary intense after infection is contracted, and hence mortality attributable to infection should increase as age increases and reproductive value declines.

(5) *Parent–offspring insulation*: clearly parental presence or parental care increase pathogenic propagation while the removal of the parent (or parental generation) through early death or migration alleviate it. The creation of an interregnum when all hosts are absent from the local environment (except in zygotic form) differentiates the successive set of environments faced by pathogens, forcing the pathogen to become dormant, adapt to non-host conditions, or to adapt to the developmentally differentiated

zygotic stage. Semelparity and host dormancy may be, in part, adaptations to pathogens.

(6) *Dispersal*: the greater the dispersal of an individual, the greater the genetic distance between it and the other individuals closest to it, and the lower the cross-genotypic correlations. Also, depending on the nature of the parasites, there will be some likelihood of having escaped from those most closely adapted to the disperser's genotype in the process of dispersal. Similarly, the avoidance of conspecifics and the interposition of non-conspecifics in the path of the replicating pathogen complexifies the sequence of environments faced by parasites.

Conclusions

Stimulated in particular by Van Valen's (1973) Red Queen hypothesis, there has been increasing awareness that the continuing evolution of competitors, predators, and parasites may be relevant to the evolution of sexual reproduction (Maynard Smith, 1978; Glesener & Tilman, 1978; Levin, 1975; Tooby, 1977). As the relationship is generally envisioned, sex accelerates evolution in a coevolutionary race. However, it is not clear that sexuality does, in fact, accelerate evolution generally (Thompson, 1976), and if it did, all participants in a coevolutionary race would be sexual. The identification of relative generation time is fundamental in isolating the pathogens as the rapidly adapting environmental element which poses the primary selection pressure sexuality defends against. The emergence of long-lived multicellular organisms may have depended upon the evolution of sexuality. In the hypothesis presented here, it is not necessary for sexuality to accelerate evolution; its most puzzling feature, the rapidity with which it breaks up coadapted genotypes, becomes its chief virtue when it is recognized that a linked genetic complex quickly becomes a liability given the rapid adaptation of pathogens. The advantage of sex is not that it accelerates evolution by adapting the host to the pathogen, but rather that it genetically differentiates kin, greatly increasing within-progeny variance. Sexual recombination, by making adaptation to one host negatively correlated with adaptation to others, gains its advantage from immediate diversification rather than by increasing across generation adaptability or evolutionary potential.

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ADDENDUM

After this paper was submitted, W. D. Hamilton sent me two highly stimulating papers, now published (Hamilton, Henderson & Moran, 1981; Hamilton, 1980), which dovetail well with this analysis. The complementary approach outlined in them involves a family of mathematical models showing that given the existence of population-wide cross-generational randomly fluctuating or cyclical selection pressures (and certain other conditions), advantages to sexual over asexual forms can be shown. Limit cycles, created by paired antagonistic polymorphic species (especially where one was parasitic on the other) were particularly conducive to this. This was particularly true if there was over-reactivity in the relationship. Linkage disequilibrium, population cycles, minimum fecundities, and rapid reversals in parasite or antagonist population-wide genotype appear to be necessary to this approach. It is reassuring to find that, even starting from different premises about genetic and ecological conditions, and approaching the problem from the population rather than the kin level, they converge on similar conclusions concerning the potential role of pathogens as a force in the maintenance of sex.