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Evolution

Sexual reproduction as an adaptation to resist parasites (A Review)

(evolution/recombination/population genetics/evolutionary genetics/disease resistance)

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ABSTRACT **Darwinian theory has yet to explain adequately the fact of sex. If males provide little or no aid to offspring, a high (up to 2-fold) extra average fitness has to emerge as a property of a sexual parentage if sex is to be stable. The advantage must presumably come from recombination but has been hard to identify. It may well lie in the necessity to recombine defenses to defeat numerous parasites. A model demonstrating this works best for contesting hosts whose defense polymorphisms are constrained to low mutation rates. A review of the literature shows that the predictions of parasite coevolution fit well with the known ecology of sex. Moreover, parasite coevolution is superior to previous models of the evolution of sex by supporting the stability of sex under the following challenging conditions: very low fecundity, realistic patterns of genotype fitness and changing environment, and frequent mutation to parthenogenesis, even while sex pays the full 2-fold cost.**

Parasite coevolution will be shown to be superior to previous models of the evolution of sex by supporting the stability of sex under the following challenging conditions.

(*i*) *Very low fecundity as in scarabs and humans.* In previous modeling (1, 2), it has been found easy to show an advantage to sex when fecundities and mortalities are high, as for example in reproduction of trees, fungi, and marine invertebrates. Difficulties with low fecundities (as in humans) have been much greater. One author has suggested that sex is inherently unstable in such groups and that its retention is due to the difficulty of mutation to parthenogenesis (1).

(*ii*) *Realistic patterns of genotype fitness and changing environment.* Attempts to cope with low fecundities have had to use high fitness differences entailing dramatic changes per generation (2–5). When more realistic assumptions and values were applied to a model that used two recombining loci (3), the model failed (6).

(*iii*) *Frequent mutation to parthenogenesis, even while sex pays the full 2-fold cost.* Authors have pointed out that mutation to efficient parthenogenesis is unlikely and seldom seen and have claimed that this reduces the problem (1, 7, 8). Situations where parthenogenesis would be an advantage are extremely numerous, however, and routine successful parthenogenesis, including facultative use of the mode, has evolved hundreds of times in both plants and animals (5).

(*iv*) *Very broadly overlapping generations as in trees and humans.* Coevolutionary models of sex (3, 4) depend upon intrinsic oscillation and are sensitive to factors creating or reducing lags in feedback. Sequential (iteroparous) reproduction dissipates fluctuation. No models have hitherto met the challenge of this pattern, which is common in fully sexual organisms.

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Parasites and Sex

Parasites are ubiquitous. There are almost no organisms too small to have parasites. They are usually short-lived compared to their hosts, and this gives them a great advantage in rate of evolution. Thus antiparasite adaptations are in constant obsolescence. To resist numerous parasites, hosts must continually change gene combinations (3, 9–21). Contrary to the assumption of the mutation theory (22, 23), the host species needs to preserve not one ideal genotype but rather an array. In the course of this preservation, selective changes in the midrange of gene frequency must be common. Because single and multiple heterozygosity is maximal for genes in the midrange, the effectiveness of events of recombination in uncoupling these changes is great, thus providing power to the model that we now describe.

We simulated a host population of 200 individuals that are either sexual hermaphroditic or else all-female and parthenogenetic; the difference is controlled by a single gene.‖ All are of equal fertility in the sense that chances to be a parent in each year are assigned fairly to all living mature individuals. However, sexual parents are paired and share offspring. Therefore they reproduce their genes with only half the efficiency of asexual parents and "fair assignment" as above embodies the 2-fold advantage of parthenogenesis. In fact, in the absence of selection through differential mortality, the population extremely rapidly eliminates the allele for sex. It should be noted, however, that we are assuming males or male functions do not contribute to the number or biomass of offspring; otherwise, the mated pairs would have more nearly an average of two offspring born when the lone parthenogen has one.

The population is assumed to be at a stable density with an average death rate $d = 1/h = 1/14 = 0.0714$ per individual per year applying at all ages. Reproduction is assumed to occur on birthdays, but there is a juvenile period of $j = 13$ years during which individuals do not reproduce; thereafter, at exactly age 14 the "fair chance" to participate in reproduction begins and continues indefinitely. For a population of stable age distribution under no selection, the mean level of fecundity needed to replace deaths is easily found by summing geometric series as in standard theoretical demography to be $f = d/(1 - d)^{j+1} = 0.2016$ per individual per year (see also ref. 24); the mean age of parenthood (a measure of generation length) is $G = j + h = 27$. The particular parameter values above are chosen to imitate primitive hominid reproduction.** Among the parameters so far defined, *d*

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‖Complete program documentation is available from W.D.H.

**Humans have paternal care whereas, to judge from skeletal sexual size differences comparable to those of baboons and gorillas, male australopithecines probably did not. A 2-fold cost of sex thus might be appropriate to primitive hominids; in any case, it applies a conservative test of the model.

The more general motivation for using sequential (iteroparous)

(accompanied by its h) is different from all others in that, although it is fixed as a mean for the population as a whole, it varies over individuals according to genotype because of effects of parasites: this is the sole kind of selection on hosts in the model. How the variation in mortality comes about in the model will now be described in full detail.

The host population is subject to n (2–12) species of asexual parasites; each species also has a population of 200. All parasites have $j_p = 0$ and $G_p = 0 + 1/d_p = 1.1$, so that $d_p = 0.909$. Many other combinations of the host and parasite demographic and selection severity parameters have been tried. The results, not reported here, were generally similar to those that will be described provided parasite generations remain short compared to those of the host. As expected, changes that simulated less broadly iteroparous reproduction by means of a menopause (see footnote **) placed close to the age of first reproduction made sex succeed better; thus, the schedule having a wide overlap tests a fairly difficult case.

Both hosts and parasites are haploid. Each parasite species is assigned k loci for its own chromosome. The host's chromosome has a defense sector of k loci for each of the n parasite species. Hosts also have a sex-determining locus so that total host chromosome length is $1 + nk$. Alleles are 0 and 1. Each year, every host randomly acquires one parasite of every species, n in all. A parasite's fitness is evaluated by matching its chromosome with the assigned section of its host's chromosome and counting matched alleles. Thus if the host's section reads 00110 and the parasite's section reads 01111, the sum is $S_p = 3$. The maximum here, obtained with identical strings, would be 5. To fix ideas further by a potentially realistic example of only three loci, imagine that humans are haploid but still manifest the Lewis/secretor/ABO blood group system (25, 26) except that we also reduce the ABO locus to only two alleles (say A and O). Suppose that, corresponding to the $2^3 = 8$ now possible genotypes and phenotypes of this system (of which none, on the known gene frequencies, would be very rare), there exist eight strains or species of a pathogen, each maximizing reproductive success when the states of alleles at three of its own loci match those of the host and that one unit of "match score" is subtracted from a maximum score of 3 for each mismatched allele, then this would become an example of a single "parasite defense sector" in the genome of our "*Haplohomo*," relevant to the model. Quite apart from the haploidy, the example remains fanciful in that no such complete diversity of differing microbial enemies involved with the ABO system is yet known. However, there is little doubt that infectious microbes are involved in maintaining the polymorphism; several very distinct groups of parasites, as well as strains within particular species, have already been implicated.†† In the model, match scores as described are used to determine fitnesses as follows. The "parasite score" determines both the parasite's rank among conspecifics after it has detached and is competing to survive into the next year and also the parasite's proportionate relative fecundity for the year. At the same time, the parasite's match makes a contribution to the "host score" of $k - S_p$; when all parasites are considered, the host's total score therefore becomes $S = nk - \Sigma S_p$. Unlike parasite scores, host scores have no effect on fertilities, but they are used to rank all 200 hosts; then the 14 lowest ranked (because $200 \times d$ rounds off to 14) are killed. For parasites, $200 \times d_p$ rounds off to 182, so this number are killed. The system may be described as rank-order truncating "soft" selection through mortality (2, 44).

Mating of the sexuals is at random and their reproduction is with recombination at a rate r between all adjacent loci. (For example, for a case with $n = 1$ and $k = 3$, chosen to simulate eight parasites genotypes bearing on the haploid Lewis/secretor/AO blood group system as outlined above, $r = 0.5$ could be chosen realistically because the three loci in *Homo sapiens* appear to be unlinked.) Reproduction of asexuals is faithful to the parent except for mutation. All genes in hosts, both sexual and asexual, including the sex locus, have a mutation rate $m = 0.0001$ or else, in half the runs, $m = 0.01$. All loci in parasites have a mutation rate of 0.01. This rather high rate is chosen to ensure parasite ability to relocate recombinant genotypes within reasonable time despite lack of sex—the parasite threat must be acute.‡‡

The dynamics of this model can be thought of as a group pursuit around the vertices of an nk dimensional hypercube. The parasites evolve toward maximizing and the hosts evolve toward minimizing the matching of chromosomes. Such a process both tends to protect polymorphism and gives an endlessly unstable coevolution (45–47). Trajectories of gene frequencies (and of linkage disequilibria) in our model are irregular. Gene frequency has the widest range when nk is low; as nk is raised, the amplitude decreases but the support for sex nevertheless improves. It is worth noting, however, that even our highest value of nk ($2 \times 7 = 14$) falls far short of the number of loci known to affect resistance in well-studied higher organisms. In the mouse, for example, 50 loci distributed over 17 chromosomes are known to affect retroviruses alone (48). Hence our success achieved with relatively few loci augurs very robust success as numbers are increased to realistic levels.

The most acute problem of sex is not to explain how it arose but why it does not currently disappear in view of the much greater efficiency of parthenogenesis. Therefore, except briefly in the final section of this paper where we describe one possible origin for sex, we treat only the potential for sex to resist invasion by asex. To give asex a good opportunity to invade, if it can, we assessed success by initiating the model with equal numbers of sexuals and asexuals and then finding the mean percentage of sexuals present during the last 50

reproduction is to simulate varied realistic life histories, including, if required, the extreme of once-for-all reproduction (semelparity). Another reason is to forestall the criticism that, if only semelparous reproduction had been used, with overlap of host generations, the model might have failed to cycle and led to loss of sex. The demography given is easily extended to include a menopause. If m fertile years start at age $j + 1$, the first menopause birthday is $j + m + 1$. If mean annual (interbirthday) survival is $v = 1 - d$, independent of age, the formulas of the text become modified to $f = d/\{v^{j+1}(1 - v^m)\}$ and $G = j + h - [mv^m/(1 - v^m)]$. Such formulas (found by summing appropriate finite geometric series) merely display necessary average consequences of parameters j, m, and d that arise under the given demography and are never used by the model itself. Results of runs in which m is used to set a hominid menopause are mentioned below in *Low Fertility and Penetrance*.

††Genera of microorganisms shown to correlate with various phenotypes of the human highly polymorphic Lewis/secretor/ABO system include *Schistosoma* (27), *Giardia* (28), *Leishmania* (29, 30), *Mycobacterium* (31), *Neisseria* (32, 33), *Streptococcus* (32), *Haemophilus* (34), *Escherichia*, and *Vibrio* (35), albeit some correlations may still need cautious interpretation (e.g., refs. 33 and 36). Given that blood groups—glycoproteins on blood cell surfaces or else related moieties in serum and secretions—seem at first unlikely agents of resistance, it is not surprising that other resistance polymorphisms and heritabilities, often independent also of other immune system loci, prove very numerous (e.g., refs. 20 and 37–43).

‡‡In earlier versions, parasites also had a sex locus, but if parasite generation was short, they usually, although not under all conditions, lost the sex allele almost immediately. We therefore simplified the model by dropping sex in parasites. In nature, parasites commonly retain sex at least at some stage of cycle, but this may be due to (*i*) hyperparasitism (especially likely for large and external parasites) or (*ii*) the need to combat facultative defenses of their hosts (for example by an immune system) such counter-threats being generated on a time scale nearer to the parasite's own life cycle.

years of 400-year runs. To begin the model in as natural and structured a state as possible, we ran a 70-year "grace period" before the start. During this, the coevolution proceeded, but all individuals were asexual; then at year 0, half had their sex gene changed from 0 to 1. In the runs, sex tends to succeed or fail completely. Probably this is due to the disadvantage that both sexuals and asexuals suffer when their variation is depleted at low numbers. The internal divide implied, however, is evidently not very high: transitions occasionally occur within runs from at or near fixation for asexuals to at or near fixation for sexuals and vice versa.

The results for various combinations of n and k are shown in Fig. 1. It can be seen that success of sex increases with the number of loci involved in defense against parasites. In Fig. 1*c*, it is already asymptotic to 100%, and in Fig. 1*d*, it is everywhere already near to this except when $r = 0.0$. The high level in Fig. 1*d* for $nk = 2 \times 2 = 4$ (that is, where two parasites are opposed by a total of only four loci) is particularly impressive.[§§] Equally so is the fact that success also rises steadily in almost all transects in Fig. 1 *a* and *c* as loci increase, even if it rises somewhat behind what is being achieved where, as in Fig. 1 *b* and *d*, fewer parasites have been assigned more loci. The last difference is understandable on the grounds that the sexual host can change sequences in the assigned sets of loci by recombination, whereas the parasite can only change them by mutation. In going from one parasite to a pair of loci to one parasite to each locus, it is as if the extra parasite is giving the preexisting one the ability to recombine, thus blunting the edge that a sexually recombining host has over both its enemy and its competitor. However, as Fig. 1 *a* and *c* shows, this detrimental feature of multiple single-locus resistances, which would completely nullify selection for sex under plausible hard selection, is far from doing so when selection is soft. Soft selection automatically lends, even to unifactorial resistances, an epistasis in fitness which, although changeable, is always of the "plateau-with-coal pits" form that is already known to protect variation (49); here, along with variation, it also protects sex (50).

Fig. 1 also shows that the recombination rate is not critical provided it is not extremely low. The runs described and other numerical experiments we have conducted have so far failed to show significant maxima of success for r other than 0.5. We suspect that such maxima may be demonstrated by increasing the life span of parasites nearer to that of their hosts so that cycles are longer (19, 51).

To suggest how the model achieves its results at least for the simple case of n parasites resisted each by one locus (Fig. 1 *a* and *c*), the following visualization seems helpful. A light ball floats in water; its surface is marked with the outline of a cube. At the eight vertices, single-genotype colonies of our host live and grow. The weight of the largest colonies makes

[§§]Bell and Maynard Smith (21) ran a model similar to a case of ours as at the rightmost corner of Fig. 1*c*, referring to it as their "gene-for-gene" model. They found correspondingly low success in advancing an allele for free recombination as against none (frequency rose from 10^{-5} to 250×10^{-5} in 2000 generations and then showed approximate stability). However, use of "hard" selection in their model would have contributed to low success to judge from early hard runs in ours. Our trials of a quantitative matching model similar to their claimed more successful version showed that this system rapidly dropped back in its support for sex compared to the model we present as the number of loci was increased by means of n and/or k; such reversal of success would almost certainly apply to their hard selection pair of models also.

With a 2-fold cost, it is unlikely that merely two resistance loci and moderate fitness differences, as in their tables, could advance a gene for recombination. This claim is based on findings in ref. 3 and in Fig. 1. The latter shows that with four loci, especially if paired and opposed by two parasites (right forward edge of Fig. 1*d*), and with soft selection, the chance of sex succeeding is already very much better.

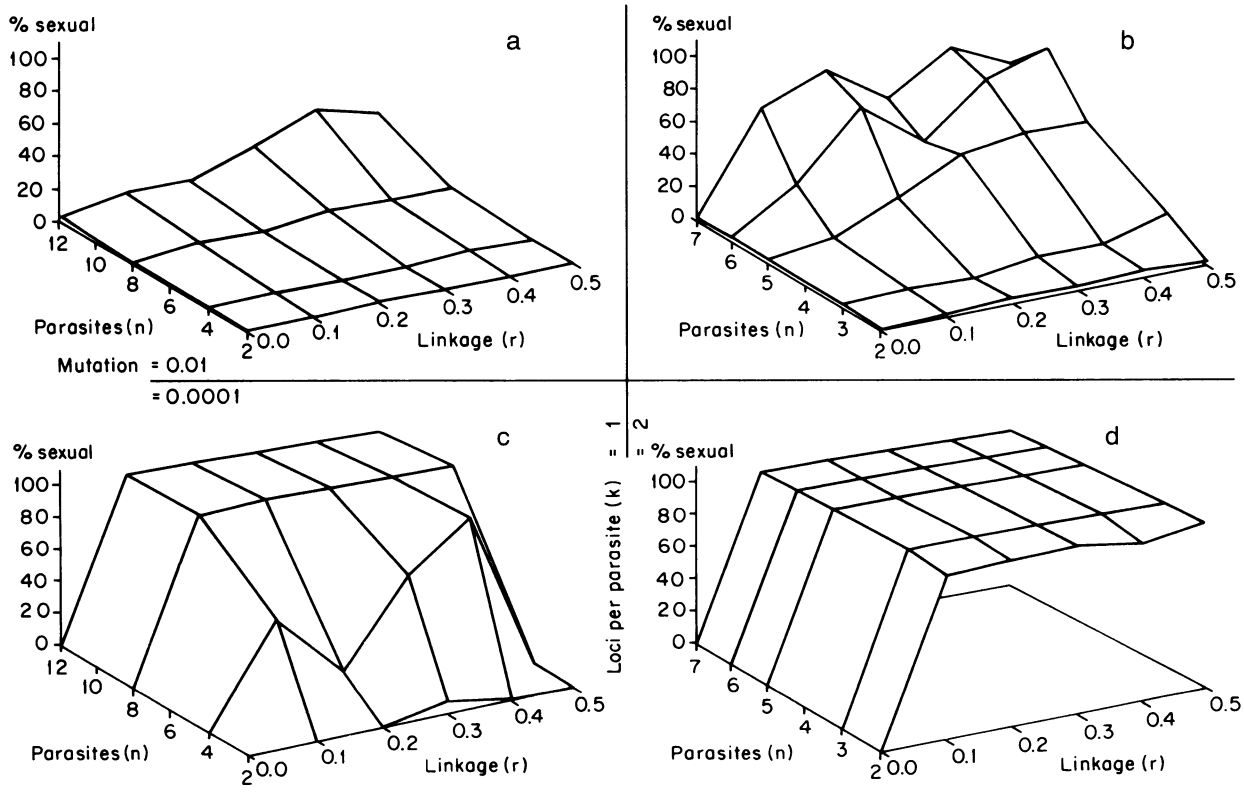

FIG. 1. Percent success of the allele for sexuality in the model. Each point is averaged over 10 runs with a population of 200. Total loci per host ranges from 2 to 12 in *a* and *c* and from 4 to 14 in *b* and *d*.

the ball turn toward the side where they are. Eventually the vertex that is heaviest goes under water; its colony is killed by the water and drops off. When the rotation caused by the previous heaviest colony has ceased, another side—the side bearing the remaining heaviest vertices, which will be, probably, those longest out of the water—begins to roll down.

If the vertices of the cube are labeled with three-locus two-allele host genotypes, 000, 001, 010, etc., in the obvious way, and if weight in the model has not to do directly with biomass of colonies but rather with an accumulation of ill health that follows upon abundance, due to coevolution, then the moving image is very closely analogous to the working of the model. We can see at once, for example, that it is important how heavily the ball rests in the water—the water line is analogous to the mortality rate. Thus, heavy mortality is likely to eliminate alleles even of the sexual subpopulation: such loss becomes inevitable, for example, if a whole face of the cube goes under at once. This emphasizes the difference of the present model from previous ones in which high mortalities were essential (1, 2) or merely highly favorable (3, 4). The previous models, however, failed to say how variability is maintained. In our model, rotation about more cornerwise axes of the unweighted cube is good for preserving polymorphism and for sex because it minimizes submergence of faces. However the most important point that the visualization makes is that no one vertex carrying asexuals is going to escape nemesis for long, because the longer a vertex is out of the water the more weight (that is, numbers, followed by parasite matching) gathers upon it.

If mutation is rare, eliminated asexual genotypes are very slow to come back. Of course, sexual genotypes at the same vertex die too, but they are by comparison very easily recreated (52). Specifically, they are brought back by matings between individuals at appropriate opposite corners. Most important, as the number of polymorphic loci (dimensions) of the model is increased, the safety of all the alleles of the sexual population increases also: each new locus with two alleles diversifies each previous genotype into two new ones, thus doubling the number of places (vertices) where carriers of an allele can remain out of the water. Alleles that survive extinction in this way always have a chance to recolonize empty vertices. By spreading from the genotypes in which they survived, the alleles again enter all combinations: sex has been their Noah's Ark.

While not essential for successful models for sex through parasitism, the soft selection by means of truncation is extremely favorable to it (50), as has been verified by comparing hard (2, 53, 54) runs of the model. Soft selection helps sex simply because, while it readily extinguishes clones (52), it tends not to extinguish temporarily "bad" alleles in sexual hosts.

Soft Truncation Selection

The power of truncation to change gene frequencies at many loci simultaneously is well known (44, 55). Under the soft truncation selection of the present model, permanent polymorphism instead of fixation arises plausibly and strongly out of the inevitable frequency dependence of the host–parasite interaction. Multilocus interaction with multiple parasites reduces amplitudes and creates situations more and more favorable to sex. This proceeds in several ways. First, multilocus polymorphism creates numerous genotypes and the possibility for every individual to be genetically unique. Every event of truncation then eliminates members of more than one genotype. It follows that currently bad alleles must often be in "good" company. Such alleles are both protected from immediate selection and unlikely to be recombined into the very low ranking classes that are subject to truncation in fewer generations than it takes for their disadvantage to be reversed. Second, frequency dependence ensures removal of genotypes that are common and that carry abundant alleles. Third, inherent lags due to generation turnover and to linkage disequilibria emphasize recent abundance over present or future, inducing overshoot and consequent tendency to cycle. The combined result of these factors is that, with increasing loci, the danger for sex ceases to be of allele extinction and lost variability and becomes rather that the model may reach multilocus equilibrium and not cycle at all. In practice, however, equilibrium is not observed: the destabilization implied by the third factor and by the truncation itself appears always adequate to keep the system mobile. Fig. 2 shows that at least under the assumed symmetrical conditions of parasite interaction, after asexuals are eliminated, gene frequency remains mostly in the midrange for multilocus runs, and linkage disequilibria are low. The conditions chosen for Fig. 2 are those where sex is maximally stable, similar to conditions on the rearmost corner of Fig. 1*d*, except for lower mutation.

To check that polymorphism continues as protected as appears in Fig. 2, a run with the same parameters was continued for 7000 generations. This ended fixed for sex and with all resistance loci still variable. To challenge the model further, a second run of 7000 generations was conducted in which mutation from asex to sex was not allowed and environmental variation was added. Mutation rates at the sex and resistance loci were made 0.001 (sex to asex only) and 0.0, respectively. Gaussian environmental variation was added to the match scores to an extent that the added variance was four times the variance expected from matching in a neutral model. The result of the test was as before except that incursions of asex were more frequent and of greater magnitude. Still, the incursions hardly every rose to half the population before declining, and still no fixations of resistance loci were observed.¶¶

The symmetry of the model that leads to gene frequencies distributed around 0.5 is admittedly artificial. However, much more generally significant and more potentially testable is the implication of episodic upward selection on minority alleles. The mutation theory (23) in contrast lacks such selection: if at all, mutant alleles only reach substantial frequencies by genetic drift. It should be possible, given some identical repeats of the by now numerous surveys of electrophoretic variation in wild populations (reviewed in ref. 56), to test for the intervening occurrence of upward and downward pressures and also reversals.

The essence of sex in our theory is that it stores genes that are currently bad but have promise for reuse. It continually tries them in combination, waiting for the time when the focus of disadvantage has moved elsewhere. When this has happened, the genotypes carrying such genes spread by successful reproduction, becoming simultaneously stores for other bad genes and thus onward in continuous succession. In contrast, asexual genotypes lost in the same phases of truncation come back much more slowly by mutation only. A lost allele that specifies a complex task-specific molecule may not come back at all.

Parasites vs. Mutation: The Evidence of Ecology

Unfortunately for checking the idea against nature and discriminating it from other views, the main contender idea, that of mutation clearance, also works best under soft truncation selection (57). Hence many of its predictions are the same.

¶¶Runs have shown that without the addition of environmental variation even a one-way mutation rate of 0.01, when combined with other parameters as in back left planes of Fig. 1, still does not result in loss of sex: some asexuals are then present at all times but generally remain at very low frequencies.

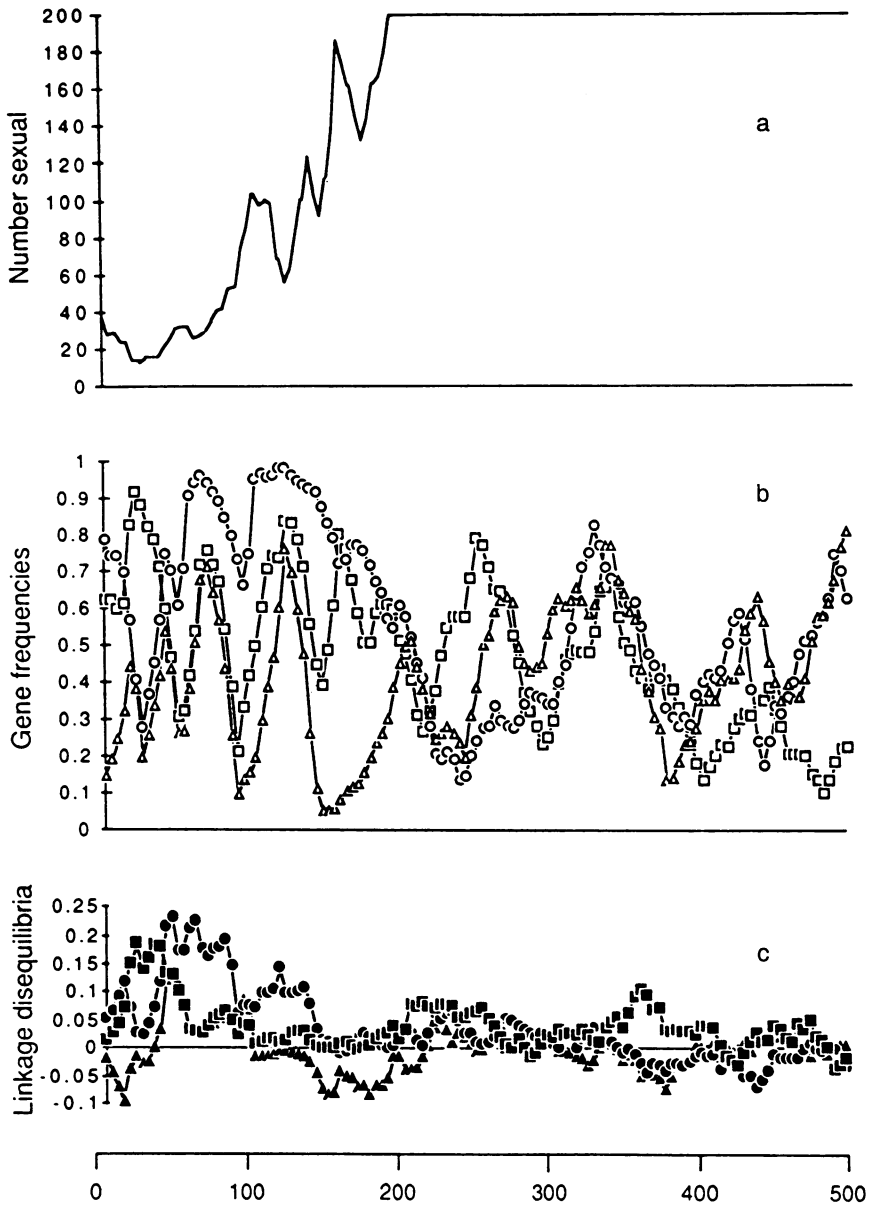

FIG. 2. Example set of trajectories in one run for gene frequencies of the allele for sex (*a*), and 3 of 14 resistance loci (*b*), and linkage disequilibrium among these three resistance loci (*c*), shown every fourth generation. Model parameters are those of the most distant corner of Fig. 1*d* and are as described in the text except that mutation rates are lower: 0.00001 for hosts (all loci) and 0.005 for parasites. The run is started with 25% sexuals.

Both theories, for example, predict that species should be most sexual when they occupy saturated habitats, compete with members of their own species, and compete by contest rather than fecund breeding. "By contest" here is meant that, while most individuals easily could breed almost as effectively as those that do, many do not breed because of lack of access to some essential prerequisite. This may be a nest hole (if a bird), territory, membership of a group, position in the canopy of the forest (if a tree), or the like. If success in contests for limiting resources is dependent on health and health depends on either mutation load or parasite resistance, both theories predict sex will win. Such a prediction does seem to be fulfilled (5, 58). Climax or "K-selected" kinds of species are usually sexual, and it is generally the "r-selected," colonizing life forms, for which contest competition is minimal, that have the wasteful male aspects of reproductive function reduced or, as in parthenogens, completely abandoned. The basis of such a prediction is, we believe, unique to these theories; however, the facts themselves have often been presented (5, 59–61), usually with different correlates such as harshness or physical fluctuation of environment suggested as cause.

It may be hoped that further details of the ecology of parthenogenesis and inbreeding may help to evaluate the two theories. However, this may not be easy, even by experiments. Both deleterious mutations and parasites make organisms sick, and both theories suggest that self-assessment of being sick, when there is a choice of sexual or asexual reproduction, ought to direct use of sex or, within sex, direct a higher rate of recombination. Thus the results of an experiment in which a population of daphnia, say, was exposed on the one hand to mutagens and on the other to parasites and in the control to optimal conditions might well come out favoring or disfavoring the theories jointly but fail to discriminate.‖‖

‖‖Both mutation clearance and parasite resistance must have outbreeding to work. Since Darwin and earlier, numerous examples

Some circumstantial evidence from nature, however, favors parasites. For example, organisms of environments expected to be mutagenic but not parasite infested do not seem to be highly sexual, but rather the converse. High levels of ionizing solar radiation in alpine habitats might be supposed mutagenic, and yet parthenogenetic and inbreeding plants are common there (5, 66). In plants more generally, the association of diminished or abandoned sexuality with the colonizing habit is particularly obvious (18, 67–75). This, as already mentioned, favors both theories against many of the alternatives. More supportive of our particular view, however, is that the association has quite often shown the expected lack of resistance to parasites when host densities rise and parasites come to the fore. A particular illustration, out of many (72–76), is the rust fungus *Phragmidium violaceum* released in Chile for control of alien brambles. One of the two bramble species, *Rubus constrictus*, is parthenogenetic, while the other, *Rubus ulmifolius*, is fully sexual and self-incompatible. The rust has severely checked the spread of the parthenogen, but it has affected the sexual very little (77).

Preserve or Eliminate

The essence of the mutation theory is that sex facilitates the elimination of unequivocally bad alleles; the essence of the parasite theory is that sex stores temporarily bad alleles and does *not* eliminate them. In our model the mutation process translates from one potentially useful allele to another. This is admittedly artificial. However, as presented in Fig. 1, it serves indirectly to emphasize the conservation aspect. When *a* and *b* are contrasted with *c* and *d* in Fig. 1, it is shown that a high mutation rate between alternative alleles for resistance hinders the success of sex. Recalling the image of the floating ball or better still thinking of an analogous floating hypercube, note that a mutation moves an individual along an edge of the hypercube. Thus this kind of mutation gives mobility to asexuals approaching that which sexuals can have through recombination and reduces the advantage of the sexuals in replacing lost types. The point also highlights the following argument and recent evidence.

If *any* change is good, evolving an increased mutation rate must be easy. It follows that if *any* new variant of a protein is effective as a tool for the host while at the same time increasing resistance to a parasite then sex ought to die out. That this does not happen indicates, in our view, that mutations creating effective new versions of a defense molecule or physiological tactic are uncommon. Such being the case, sex has the useful function of continually recombining a set of preserved defensive elements (20). Elements here can mean either parts of a complex molecular structure or parts in some more abstract sense—components of an individual's stance against all its currently pressing parasites. Current understanding of disease resistance does indeed favor existence of molecular parts that would be hard to reevolve once lost (25, 26, 78). Molecular structure coming to light in the well-studied immune system of vertebrates, for example, favors such interpretation. So too does the growing emphasis on mimicry as a factor in parasitism (29, 30, 79–88). Presumably almost any common, necessary, and exposed molecular structure on or in cells of a host can be potentially mimicked, so bringing the genetics of that structure into play.

Mutation rates of genes, as well as rates of evolution, have been suggested to be high for resistance (89–91), but there is growing evidence that this is not the only reason why defense systems are genetically so diverse. Many polymorphisms that are either known (35) or likely (92, 93) to be connected with disease resistance are ancient, spanning many millions of years and the divergence of genera (78, 94–98). This begins to be confirmed even by detailed homologies of DNA (99–101). The polymorphisms include many of the human blood groups (ABO, Lewis, MN, and Rhesus), the secretor polymorphs associated with ABO, taster for phenylthiourea, lactate dehydrogenase, phosphoglucomutase, the Gm component of polymorphism of immunoglobulin, carbonic anhydrase, and others. Esterases, by being also proteases (102), may be more connected with microbe control than their name suggests (95, 103). They are often multiply varied throughout whole sets of related species, although the variants generally remain of unknown homology. The vast and much-researched polymorphism of the major histocompatibility complex system presents a similar case and has unquestionable relevance to disease. It is now known that, far from being arbitrary badges of identity as once thought (104, 105) (for which purpose any mutant might be satisfactory), the histocompatibility proteins are more in the nature of molecular tongs designed to hold up processed fragments derived from parasite attack in order to alert and inform other cells (87, 105). Random change in such functional molecules is much less likely to be successful than recombinations of components that have already built effective structures in the past. The last claim is also likely to be true of the combinations in the Lewis/secretor/ABO system (25, 26), which contrasts with the major histocompatibility complex system in that the components are not linked.***

Although our model works best with multilocus defenses against each parasite (compare success in *b* and *d* to that in *a* and *c* in Fig. 1), our findings do not compel us to interpret the model as implying a kind of molecular Lego in nature (success is still near complete in Fig. 1*c* at higher *n*). For a sapling tree racing with conspecifics to be first to occupy a light gap in a woodland canopy, one parasite might be a new virus strain, another might be a stem-mining caterpillar with a new detoxifying enzyme, another a deer (its population rising, perhaps, because it had found a solution to a disease problem of its own), and another an exploitative instead of protective variant of a mycorrhizal fungus. The necessary correctives for these threats are quite different in character. The first, for example, may need the recombination of molecular parts (e.g., ref. 78), whereas the second and third may need change of a more quantitative kind—a thickened cuticle to prevent hatchling larvae boring in or, for the deer, more tannin in the bark. Altogether, assembling adaptations for any such upcoming set may have the same urgent requirement for recombination as the more purely molecular kind of rearrangement in defense previously outlined. Moreover, although it helps if parasites are capable of causing

of adaptation to secure outbreeding have been noted. Recently mooted theories such as DNA repair (62, 63) and rapid fixation of advantageous mutations under diploidy (64) should work as well or better under inbreeding. Even inbreeding is unnecessary and not ideal: rapid fixation, for example, could come from automictic parthenogenesis, which is potentially much more efficient (65).

***Parasites whose epistatic selection pattern is imposed through direct effect on fitness potential, rather than extrinsically, as by our truncation selection, are not yet known for the Lewis/secretor/ABO system. However, they are not unlikely since parasites (as well as pesticides) clearly sometimes impose direct epistatic patterns in other species (106, 107). In wild rabbits, polymorphism of IgG based on two unlinked genetic loci determining constant regions of the heavy and light chains reveals strong epistatic selection. This is almost certainly due to parasites and is quite likely due to the myxoma virus (78), but it is not yet possible to apportion the selection to intrinsic complex selection or/and an extrinsic soft process like truncation. If present, intrinsic epistasis probably further favors sex. Runs of our model with such epistasis added through the method of scoring matches gave even stronger support than the version we report.

severe damage, even this is not necessary. Enough parasites with small effects, each still contributing to ranking (72), can make sex secure, to judge from the trend we have shown. For example, in a gorilla or hominid (to which our life schedule gives a rough approximation), a contribution could come from resistance to the common cold.

Low Fertility and Penetrance

Extremely low fecundities in the animal kingdom are consistent with sexuality in the parasite model but not with the mutation model as it is currently specified (23). The *H. sapiens* species is usually regarded as having low fecundity, but our species does not have the lowest fecundity, by any means. Some scarabs have mean female life-time fecundities as low as five but are fully sexual and indeed show exaggerated characters from sexual selection (108–110).

To check that our model can account for *H. sapiens* or an ancestral hominid (which, by arguments based on sexual size dimorphism, would probably lack paternal care and therefore be more directly relevant to the model), we ran a menopause age of 35 and a lower mortality of 1/16 per year (see also footnote **). By combining this with 12 parasites being resisted by one locus each, with host mutation at 0.0001 and recombination at 0.3 (a midpoint on the back wall of Fig. 1*c* but with a lower, more realistic mutation rate), we found that the model still gave almost full success. The model has hermaphrodite individuals, but there is no essential difference from a version where sexual individuals are born male or female while parthenogenetic progeny, equally numerous, are all female. Hence we confidently expect the same result for a two-sexed case. Calculation shows that when sexuals dominate in this parallel version, females who live right through the reproductive period would seldom bear more than 10 offspring, while the expectation for those just entering the period is (because of mortality) about 5. This schedule is almost too infecund to be plausible for a human hunter gatherer. When we brought in the model maximum of 15 loci (triplets of loci resisting 5 parasites), at the same time lowered the mutation rate of hosts and parasites by factors of 100 and 5, respectively (i.e., going again to rates more realistic than those in Fig. 1), and set mortality to 1/35 while keeping the menopause age 35, all of which gives mean gross fertility of four, as might be appropriate to extreme scarabs (108–110), sex is only occasionally replaced by asex in runs. It would probably be replaced less often still if populations were made larger.

Even with genetic resistance diluted by large amounts of random variation, sex is still uninvadable in our model. This is confirmed by runs with environmental variance approximately equal to the parasite-induced variance (with mean gross fertility as low as three) and, as mentioned in an earlier section, even with runs having four times the environmental variance (for $n = 7$ and $k = 2$).

Mutation Rate

Keeping germinal tissues deep within a body plus using internal fertilization and viviparity might be expected to buffer germ-line chromosomes especially well. Therefore, in the mutation theory, species having such characteristics might be expected to be experiencing relaxed mutation problems and to be frequently experimenting with gynogenesis and parthenogenesis. The opposite is the case: it is prokaryotes, those organisms that do not buffer the environment at all by a surround of cell layers, or even by a layer of cytoplasm, that reject sex most completely. In spite of their exposure, their rates of mutation per generation are actually lower than those of large eukaryotes by several orders of magnitude. This together with other data (111) suggest that the mutation problem can be solved when sex is not present to help; when, on the other hand, sex is present for other reasons, mutation control can be relaxed, perhaps with long-term advantage for evolutionary flexibility.

Origins

The parasite model of sexual reproduction suggests how sex might have arisen in a natural and continuous manner, as Darwinian theory generally requires. The origin of sex as suggested by Margulis and Sagan (112) has cannibalism by primitive unicells in times of starvation that evolves to a stalemate (at least in some encounters), with would-be cannibals becoming fused but eventually separating when the conditions ameliorate. While fused, some genetic material might, accidentally at first, become exchanged. Our contribution is to suggest the important way that genes encouraging regular chromosome breakage and exchange might confer advantages to their possessors, by means of the newly created gene combinations. We suggest that eventually the new combinations proved their worth mainly during unwanted contacts with smaller unicells that were specialists in exploitation—incipient parasites.

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