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0014-4754/85/101235-11$1.50 + 0.20/0

The adaptive significance of sexuality

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Summary. A theory of sexuality and polymorphism is proposed in which diversity at the molecular level is the adaptive response of multicellular organisms to the challenge of microparasites that have smaller genomes, shorter generation times and which can evolve more quickly than their hosts. The theory has implications for genetically homogenized crops and other cultivated plants as well as for immunology. A different function of sexuality is proposed for microorganisms that reproduce both asexually and sexually. Several possible experimental tests are discussed. Mathematical modelling techniques are outlined qualitatively and compared with game-theoretical methods which may be interpreted as simplifications of population dynamic and genetic equilibria. Some results about equilibria, stability and extinction in the population dynamics of polymorphic host-parasite populations are referenced.
Key words. Recombination; sex; parasites; pathogens; immune system.

1. Introduction

Birds do it, bees do it, plants, algae, protozoans, bacteria, and last but not least: mammals and *Homo sapiens*. Much of the entire biosphere is engaged in sexual recombination. The near universality of sexual recombination lets one suspect a common cause or function.

It has been argued that sex speeds up evolution by bringing together rare advantageous mutations[26, 27, 63]. Kimura and Ohta[42] have stated this effect dramatically: 'Sexual

reproduction has played a very important role in speeding up evolution in the past, helping to produce man before the sun in our solar system burns out.'

Lewontin[53] said that sexual recombination creates the variety which constitutes the potential of further evolution, while E.O. Wilson[91,92] describes its role as creating variety as insurance against changing environments.

Until the mid-sixties these effects of sexual recombination were often taken as an explanation: it is good for evolution, hence nature invented sex (comp. Felsenstein[26]). The only remaining question was: when? Thus one may find in many works on the origin of life speculations about when sexual recombination was invented. Once this happened evolution could proceed to create man.

Sex thus is explained through its purpose. The end explains the means. Biological methodology quite generally observes a taboo against explaining biological facts by the ends which they serve (comp. Fraenkel and Gunn[30]). However, biologists often have not hesitated to enshrine evolution itself as the ultimate and final cause of all things biological.

The trouble is that what is good for evolution need not be good for the individual. If sex is bad for the individual but good for evolution in the long run, what prevents individual mutants from pursuing their own fitness advantage by reproducing asexually? Many microorganisms can reproduce both asexually and sexually. Plants can spread by vegetative propagation and many species can produce seed without being fertilized by pollen from other plants. Mutations that turn off the complicated machinery of sex are possible, and many eggs can be made to develop without fertilization by sperm. There are parthenogenetic species of salamanders and fish. Parthenogenetic plant species are frequent and often successfully invade the territories of their sexually reproducing ancestors and relatives. (For details on parthenogenesis see Maynard Smith[59], Cuellar[23].)

Maynard Smith[59] has pointed out that a parthenogenetic mutant producing only females has an initial 2:1 fitness advantage over its sexually reproducing competitors. Why then do parthenogenetic varieties not replace sexual ones? This is the fundamental problem. (Actually, the 2:1 advantage holds under-*ceteris paribus* assumptions. It is assumed that lifetime fitnesses of sexual and asexual types are unaltered except with respect to the sex of the offspring. This is often not the case.) If the assumption is satisfied, then the percentage of parthenogenetic females in a population initially about doubles with each generation. Subsequently the mutant allele keeps on spreading (though at reduced rates) until it asymptotically approaches 100%[59]. If parthenogenesis leads to reduced fecundity, parthenogenetic mutants would still take over as long as the advantage is better than 1:1. (A further complication is the phenomenon that in contrast to parthenogenetic lizards, fish, insects, and numerous plant species there are no parthenogenetic birds or mammals among 12,000 species. Why?)

If the benefit to evolution at large (to evolve man before the sun burns out) were the driving force that maintains sex against individual fitness advantage, it would be a case of group selection: the group being the entire biosphere. What mechanisms would prevent individual parthenogenetic mutants from spreading? Unless we believe in replacing divine intervention by an equally mystical force of intervention guided by the presumed long-term goals of evolution, we must account for the persistence of sex in terms of individual fitness advantages or in terms of mechanisms that prevent parthenogenesis from taking hold. These mechanisms in turn would have to be explained as evolutionarily stable, or as being stable over long periods of time.

Many attempts at understanding sex have been made (comp. Williams[90], Shields[77], Bell[8]). In his monograph, 'The Evolution of Sex', Maynard Smith[59] writes in the preface: 'I am under no illusion that I have solved all the problems which I raise. Indeed on the most fundamental question – the nature of the forces responsible for the maintenance of sexual reproduction and genetic recombination – my mind is not made up ... it is not clear to me whether the short-term selective forces I discuss are sufficient to account for the facts, or whether models of a qualitatively different kind are needed.'

The models discussed by Maynard Smith are based either on temporal changes in the environment or on spatial heterogeneity (unpredictability). He concludes (p. 89): 'At equilibrium in a uniform environment if there is any selection on recombination it will be for reduction.'

This suggests that species in environments that have remained temporally and spatially homogeneous for extended periods of time should have a preponderance of asexual and parthenogenetic species.

It appears that off-shore marine environments, especially deep-sea environments, are highly uniform. Yet sexually reproducing species flourish there as elsewhere. (A careful tabulation of data on sexuality in exceptionally stable environments would be in order.)

Hamilton[33,34], Jaenike[36] and Bremermann[11] (independently) have pointed to another force that could favor sexual recombination in multicellular organisms: microparasites that cause disease. (Rice[74] has made a similar suggestion, he emphasizes the transmission of parental pathogens.)

Microparasites (broadly defined to include viruses, fungi, bacteria and protozoans) have shorter generation times, smaller genome sizes and have greater speed of adaptability than their multicellular hosts. These parasites depend for their own survival and propagation upon their hosts. For example, viruses cease to replicate when the host dies. This creates a feedback between host and microparasites with a population dynamices of its own (comp. Anderson[2], Anderson and May[3–5], May and Anderson[56]). We propose that the key to understanding sexuality, as least in multicellular organisms, lies in this feedback between microparasites and their hosts and in the different rates with which hosts and parasites can adapt through mutations and other genetic changes. We discuss this proposal further in the following sections. (For another discussion see B. Levin et al[47].)

A different mechanism may be responsible for the maintenance of sexual recombination in single-celled organism: Some microorganisms live indeed in unpredictable environments and environments that change with the seasons. Bacteria repress genes that are not used. For example, *E. coli* represses transcription of the beta-galactocidase gene when there is no lactose in the growth

medium. The gene can remain repressed for many generations when no lactose is present. Similarly other genes remain repressed for generations until their function is needed again by a change in the environment.

While genes are repressed they are not subject to purifying selection. Thus even when the mutation rate per cell division is low, the cumulative rate in an unused gene can be high. It is proportional to the number of generations that have passed since last used.

E. coli can go through three generations per hour, 72 generations per day. After several days mutations have accumulated in the repressed and unused genes. When the environment suddenly shifts and repressed genes are derepressed, they may no longer function. At this point there is an advantage in exchanging genes with another individual. For example, if each donor carries one nonfunctional gene (at different loci, and assuming that the loci are not too closely linked) then there is a chance, up to 25%, that the recombinant genome is fully functional. A 25% chance of producing fully competitive descendants is better than producing no competitive descendents at all. Thus for microorganisms sexual recombinations may be something like a repair mechanism.

Note that *E. coli* reproduces normally through asexual division. Only occasionally will it shift to sexual reproduction where a copy of the genome is transferred to another bacterium through a sex-pylum. Transfer of the genome takes 90 min (versus 20 min generation time for asexual reproduction under favorable conditions). (Comp. Lewin[51].)

Yeast normally is diploid and reproduces asexually through cell division. On occasion yeast produces haploid cells of two different mating types (a and alpha). Cells of different mating types are chemotactically attracted to each other and fuse, forming diploid cells which then divide asexually for many generations[52].

The sex-as-repair model for single-celled organisms was proposed in an appendix to Bremermann[10]. (Note that portions of the paper, notably the section on the generation of antibody diversity have been made obsolete by recent developments in immunology. The appendix on sex as a repair mechanism remains valid.)

Our model could be tested by subjecting continuous colonies to environmental shifts and by manipulating mutation rates through mutagenes or UV. Also, sexual mechanisms require resources. In the absence of any benefits from sexual recombination one would expect that asexually reproducing mutants would prevail. Hence, in a steady environment that is spatially and temporally homogeneous, and in the absence of parasites (such as phages) one would expect asexual mutants to take over.

Besides the exchange or diploid association of entire genomes there is a lively trade of smaller pieces of DNA. In addition to the main chromosome many bacteria contain plasmids which are small, independently replicating circular pieces of DNA. Plasmids are also found in eukaryotic cells like yeast. They are easily acquired and lost. Plasmids are essentially parasitic since they are replicated at the expense of their hosts. Often they also carry genes that are beneficial to their hosts like resistance factors, for example genes for endonucleases that provide protection against invading phages. Like phages, plasmids may on occasion become integrated into the genome. Lysogenic versus lytic infections are advantageous to the phage, depending upon circumstances[13]. The population dynamics of plasmids has been discussed by Stewart and Levin[81], Novick and Hoppenstaedt[67], Van der Hoeven[85], and Hockstra and Van der Hoeven[35]. For the molecular biology of plasmids and phages see Lewin[51].

2. Pathogens are not just another factor in the environment

Pathogenic parasites are a powerful factor of host survival and fitness. For example, prior to the advent of modern hygene families typically lost half their children to intestinal and other diseases before the onset of puberty. Today, malaria is endemic in many countries. Trypanosomiasis excludes cattle from wide stretches of Africa[5]. The American chestnut *(Castanea dentata)*, which at the beginning of this century constituted 25% of Eastern forests, has been virtually wiped out by a fungus[84]. The list could be continued indefinitely.

Most pathogenic microparasites are species specific and are thus produced by the very population which they attack.

While multicellular predator-prey species evolve on comparable timescales, microparasites do not. Many microparasites have an advantage in speed of adaptability by orders of magnitude. They have shorter generation times, smaller genomes and greater genetic flexibility than their hosts. For example, viruses can acquire host genes, bacteria acquire, maintain, insert, and delete plasmids beyond and above the regular mechanisms of mutation and recombination.

The speed of adaptability of microparasites is difficult to compute theoretically. It may be seen, however, in involuntary experiments with agricultural crops such as wheat and corn. When a new variety has been created by plant breeders which is resistant to all existing strains of rust or leaf blight fungus, a mutant strain of fungus tends to appear after a few years that spreads like wildfire and may ruin an entire crop. This has happened repeatedly[64].

A natural host population that is infected by a pathogen would fall to a low density until infective and susceptible individuals are at an equilibrium. If the host population falls below the equilibrium, fewer parasite propagules are produced and fewer individuals are infected. Hence the host population increases. When the host population exceeds the equilibrium, the percentage of infected individuals rises – with the effect that the host population decreases. In this way hosts and parasites can fluctuate stably around an equilibrium. (For a mathematical analysis see Anderson[2], Anderson and May[3,4] and May and Anderson[56]).

With time the parasite may evolve towards an optimal level of virulence that balances the inevitable damage to the host resulting from the parasite's replication and shedding of propagules (damage to tissues leaves, etc.) against the cumulative advantage of shedding propagules throughout the host's lifespan. The longer the host lives, the more propagules are shed (comp. Bremermann et al.[15]).

Parasitism, even highly coevolved parasitism, is never beneficial from the host's vantage point. An infected host suffers excess morbidity and/or reduced fecundity and thus a reduction of fitness.

A mutant host that is not subject to infection by the parasite thus has higher fitness and would increase to levels determined by the carrying capacity of the environment. If the disease-free host strain is genetically homogeneous (which would be the case with an asexually reproducing clone) then it could become a target for a mutant parasite strain that would neutralize the host mutation.

This process may continue until a polymorphic host population and corresponding polymorphic collection of parasite strains has evolved. *This phenomenon should be observable experimentally in E. coli populations grown from a clone and infected with a clone of phages.*

Host resistance against parasites can be cellular and systemic. The vertebrate T cells and B cells constitute a systemic defense. At the cellular level it is molecule against molecule. We show below that sexual combination of alleles from a polymorphic host population are an essential ingredient of both cellular resistance and systemic immune defenses.

3. Host-parasite interactions at the molecular level

Both systemic and cellular defenses involve molecular interactions of great specificity. Currently many studies are underway that identify the effects of amino acid substitutions upon antibody binding and virus neutralization. Monoclonal antibodies have made possible serological specificities that one could only dream of with multiclonal sera.

Single amino acid substitutions in viral proteins can change the serological identity of a virus strain[45]. Conformational changes that are induced by amino acid substitutions are being studied by X-ray diffraction analysis and computer studies of variations in amino acid sequence. A picture of several critical sites on viral proteins emerges. At the critical sites substitutions affect serological specificity while other portions of the polypeptide chain are less sensitive[89].

Epidemiological studies trace the variety and antigenic shifts and drifts of common infectious diseases such as influenza, hepatitis, polio, measles, etc. The variety of viral strains and their genetic drifts and shifts are of prime importance for recurrent epidemics as well as for the preparation of vaccines for immunization. For a recent survey see Chanock and Lerner[19].

The processes that bring about antigenic drift and shifts are very complex. In the case of influenza human populations throughout the world as well as animal hosts participate in this process. It would be unreasonable to model such a complex process. Instead it seems appropriate to accept the appearance of new strains as an empirical fact, to determine the time it takes for new strains to appear, and to model their effect upon host populations. This is the approach which will be taken in the mathematical models that are discussed in section 10.

The molecular battles between hosts and parasites are not limited to systemic immune defenses but take place at the cellular level as well. The principles of host-parasite dynamics have been studied theoretically and experimentally in cultures of bacteria and bacterial viruses. Here the binding of a bacteriophage to a receptor site is highly strain specific. The battle between host and phage involve host mutations that abolish binding of a phage strain and mutations in the viral capsid protein that restore it[51, 80]. Once a virus particle has been absorbed, its RNA or DNA enters the cell where it faces nucleases[7]. The restriction nucleases of DNA are site specific, and restriction sites are characterized by short palindromic DNA sequences[52]. Any invading DNA that contains a restriction site gets degraded. Mutant viral strains that do not contain the restriction site can infect the host. However, hosts can acquire new genes for different restriction nucleases. The evolution of bacterial host-parasite systems can be observed in chemostat experiments. It happens quickly and would lend itself to the testing of theoretical predictions, such as the emergence of polymorphic populations with different strains of hosts and phages (comp. section 10).

Similar specificities affect the binding of fungal toxins to specific targets in the host cell[75, 82, 83]. Plant molecular genetics is a very young field. Advances in molecular biology, especially gene cloning and sequencing of parasite genomes, have made it possible to study host-parasite interaction at the molecular level. The polymorphism of both hosts and parasites is becoming apparent (comp. Verma and Hohn[87]). The full range of host-parasite interactions at the molecular level is rather complex[31]; however, in some cases susceptibility and resistance depends only upon a single locus in the host and a corresponding single locus in the parasite. Such correspondence is known as gene-on-gene resistance.

4. Gene-on-gene resistance, sex and polymorphism

Gene-on-gene resistance is a widespread phenomenon for cereal grasses and their pathogens. Mode[61,62] pioneered models of such coevolving systems. Numerous similar models have been studied subsequently[37, 48, 50, 93].

Flor[28, 29] investigated the genetics of the interaction between flax *(Linum usitissimum)* and rust *(Melampsoa lini)*. He found that there were 27 genes for resistance (R genes), distributed as multiple alleles at five loci. Resistance is inherited as a dominant character. Virulence in rust is controlled by a complementary system with a one-to-one relationship of each R-gene in the host with a corresponding gene in the parasite. Virulence is recessive. (This is a somewhat idealized picture. For a recent review of the genetic and biochemical basis of virulence see Panopoulos[68].)

Such a gene-on-gene relationship was been found in many other host-parasite systems[72, 73]. Pimentel[73] and Bremermann[12] have argued that the evolution of gene-on-gene relationships resembles the response of parasites to other single environmental stress factors, such as pesticides or antibiotics.

Gene-on-gene resistance is frequently encountered in fungal plant diseases. For example, cereal rust damage their hosts by injecting hyphae to collect nutrients. They kill host cells for food. Damage to the host may be severe[86]. A virus, in contrast, requires live host cells for its own reproduction.

Fungi often produce toxins that disrupt host cells. They may interfere with membrane transport or with enzymes in the metabolic machinery of the cell. It is a battle of

molecules against molecules. For example, Strobel[82,83] showed that susceptibility of sugarcane to the fungus *Helminthosporium sacchari* involves the binding of a toxin, helminthosporoside, to a membrane protein. A resistant variety had a protein that differed by four amino acids.

For diseases with gene-on-gene resistance we thus envision a battle of adaptation between host and parasite. The parasite evolves molecular species that bind, the host evolves proteins that do not bind. Here is an analogy to the immune system except that the roles are reversed: In the immune response the host produces molecules that bind and the pathogen loses if it is bound. In gene-on-gene resistance there is the added constraint that host molecules still must perform their function as enzymes or membrane proteins. The selective pressure creates *isozymes which are neutral mutations with respect to the metabolic or membrane function which they serve.*

A sexually reproducing host, drawing upon pollen from a polymorphic host population, produces seed with a variety of allele combinations. The risk that a particular allele will become susceptible through pathogen adaptation is thus spread widely. Fungal strains may evolve that overcome resistance for some of these alleles. The majority of seed, however, will carry alleles that remain resistant.

As fungal strains evolve that overcome resistance for some alleles, these alleles will become rarer. On the other hand new mutant isozymes that arise in the host population which confer resistance will spread. (For a discussion of mathematical models of this type of dynamics see section 10.)

In contrast, without sexual recombination, a host variety creates a genetically homogeneous clone. This clone is a target for pathogen adaptation, especially if it successfully proliferates (comp. Rice[74]). The situation resembles that of a cereal grain variety that at the beginning is resistant to all strains of rust and which is planted in large populations. The length of time till resistance is lost may vary. For highly homogeneous crops like wheat[6] and tobacco[54] the period of grace is only a few years. The parthenogenetic mutant thus will enjoy a period of reproductive success after which most of its descendents are wiped out by disease.

In contrast, the plant that reproduces sexually in a sufficiently polymorphic population is hedging its bets: Some seeds may be worse off with foreign alleles, but the majority will be resistant to all fungal strains, and so on for subsequent generations. Bet-hedging is not limited to the uncertainties of encountering different strains of parasites. It is a wider phenomenon in the context of strategies under uncertainty[79]. The concept of 'strategy' is well defined in the context of game theory.

Sexual recombination thus is a strategy in a game of molecular persuit and evasion. The game puts a premium on speed of adaptation. Here the microparasites are at a definite advantage. It means that parasites must be genetically flexible. Some pathogenic fungi have indeed been described as 'genetically highly unstable'[54].

The host, in contrast, is at a disadvantage in speed of adaptation. It compensates by existing as a polymorphic population, polymorphic at loci whose products are directly affected by corresponding gene products of the parasites. The contest between parasites and hosts thus can be described as a game of pursuit and evasion between two fundamentally different contestants.

Sexual recombination and polymorphism thus must be seen together. Separately they pose seemingly unresolvable problems. Together they are a mechanism by which multicellular species hold their own in their battle with microparasites.

The fertile crescent in the Middle East is the origin of many of our cereal grasses. Despite favorable conditions for pathogen growth the crops there have been relatively stable and free of epidemics[17,25]. In contrast American cereal crops have been beset by periodic crop failures and are subject to genetic management that attempts to stay one step ahead of disastrous outbreaks of cereal rust and similar epidemics[6]. Several authors have argued that this disparity is due to the genetic oversimplification of American agriculture[11,12,17,18,73]. It is important, however, to see that this phenomenon is not an isolated one but part of a general principle. The game of pursuit and evasion is general.

5. *Game models of pursuit and evasion*

Mathematical genetics has had unusual difficulties explaining polymorphism in natural populations. In a recent survey on the evolutionary dynamics of genetic diversity[55], Nevo et al.[66] have compiled a vast amount of data on polymorphisms in natural populations of plants and animals, vertebrates and invertebrates. They have correlated the measures of heterozygosity with all kinds of important biotic variables with one exception: pathogens.

In the same survey, Cook[21] describes the phenomenon of genetic diversity as 'The Problem'. It has resisted understanding within the framework of mathematical genetics for some time. Solbrig et al.[78] write on page 46: 'One of the unresolved paradoxes of modern population biology is the apparent high level of heterozygosity in populations which is impossible to account for under present single gene models with selection.'

Several theories have been proposed, most notably the balance theory[53], the neutral theory[40-42,65] and various models of frequency dependent selection[20].

Our model combines features of all three: Since gene-on-gene resistance tends to be dominant, heterozygotes have a selective advantage. Secondly, alleles that represent different conformations of an enzyme or membrane protein and which differ in their resistance/susceptibility to pathogen strains should be selectively neutral with respect to their metabolic function. Thirdly, the probability of appearance of a parasite mutant to which a previously resistant allele is susceptible rises when the allele is common. Hence, in the long run selection is frequency dependent.

Our model differs fundamentally from conventional models by including feedback between host and parasite. In classical models the selective value (usually denoted by W) is static or varies randomly in space or time. In our model the host population itself causes delayed changes in W.

Our model is a game model: Both host and parasite must optimize their fitness. Fitness of both host and parasite, other things being equal, is proportional to the host's

lifespan. The parasite also must optimize that rate at which it sheds propagules (spores, virions, etc.). This objective conflicts with longevity: the greater the rate of parasite reproduction the greater the damage to the host. A high rate exacts a toll from the host and shortens its lifespan. This game model has first been proposed by Bremermann[11]. For a further discussion see Bremermann and Pickering[14].

May and Anderson[57,58] and Levin[49] have pointed out the importance of combining population dynamics with genetics. Unfortunately the monster of intractibility raises its ugly head as soon as these models are written down. *To remedy the situation we propose that host and parasite genetics do not deserve to be treated on the same footing.* Parasites have short generation times, large populations, produce vast numbers of spores and have unusual modes of mutation and genetic modification[76]. Once a mutant parasite appears that can attack a frequent host genotype it spreads rapidly. This is demonstrated by the numerous instances of catastrophic diseases in artificially homogenized agricultural crops and garden plants[12,43].

Instead of keeping track of all individual genetic events in the parasites we treat mutants as singular perturbations of the systems equations that occur from time to time. We characterize mutants by their phenotypic ability to attack one of the existing host genotypes. (For a discussion of formal models see section 10.) What matters is the frequency with which such mutants appear and how their appearance depends upon allele frequencies of the host population. Once such a mutant appears the system goes through a transient and may settle down at a new equilibrium.

Formulating these models is fairly straightforward. They can be simulated on moderately fast computers (for specific values of the parameters). Analytical results, however, due to the nonlinearities, are difficult to obtain and are in any case beyond the scope of this paper. (Results for special cases have been obtained by Bremermann and Fiedler[16] and Bremermann and Thieme[15].) (Comp. section 10.)

We have so far focussed mainly on fungal diseases in plants and have demonstrated how sexual recombination in a polymorphic population is a strategy by which hosts can compensate the advantage of faster adaptation enjoyed by the parasites. Polymorphism and recombination are also crucial in other host-parasite encounters.

Vertebrates have a lymphocyte immune system which fights viruses, fungi, bacteria, and protozoans. In the following we will show that for the functioning of the vertebrate immune system recombination of alleles from a polymorphic population is indispensible. The alleles in question are the alleles of the major histocompatibility complex (MHC). Their combination gives individuals an immunological identity of self versus non-self. This identity is necessary since in a homogeneous host population parasites could adapt to camouflage. Again, the disparate speed of adaptation between microorganisms and metazoans is the crux of the matter.

6. The vertebrate immune system responds to rapid pathogen evolution

Vertebrates possess in addition to cellular defenses a systemic immunological defense: the lymphocytes. They are a specialized cell population, in humans, that consists initially of at least 10^6–10^7 distinctive subclones. The lymphocytes that circulate in the blood stream are screened to be self-compatible: They do not attack the organism's own cells, while they respond to foreign antigens of all kinds: viruses, bacteria, fungi, as well as cells of another individual from the same species. To escape attack from the lymphocytes, a cell must carry a specific combination of histocompatibility antigens. These differ from individual to individual (except for homozygous twins).

The total number of cells in a human organism is of the order of 3×10^{14}. If we divide this number by 10^7 (the approximate number of lymphocyte clones) we obtain an upper bound of 3×10^7 cells per clone. Since lymphocytes amount to only a fraction of the cells of the organism, the actual number is more like 10^4–10^5.

When an antigen invades, two things can happen, depending upon the relative numbers of invaders and defenders: If the number of invading antigens is small, they are bound by lymphocytes and eliminated. When the number exceeds the number of lymphocytes and immunoglobulin molecules that they can produce, then the invader has a chance to multiply. At the same time the specialized clone whose antibody binds to the invader is stimulated to proliferate. Initially the responding clone cannot produce enough antibody to bind all invading pathogens, and the pathogen population expands. (In other words there is a threshold effect, depending upon the size of the inoculum.)

Lymphocytes that bind antigen are stimulated to proliferate: a competitive proliferation results. The pathogen population expands until so much antibody is produced that more pathogens are destroyed than are being born. At this point the balance tips in favor of the organism: the pathogen population declines and the organism can recover (comp. Perelson et al.[69,70]).

The invading pathogens can be compared with an invading army. If the invading army is small, it is eliminated before it can proliferate. Otherwise, the battle becomes one of competitive proliferation. One may ask: Why are infections necessary in the first place? Why aren't organisms adapted to have sufficiently large lymphocyte clones to begin with?

This is a logistic problem: it depends upon the number of different kinds of pathogens that can assault the organism. For each potential pathogen the organism must have an 'army' of specialized lymphocytes. The number of different armies, that is, the number of different kinds of lymphocyte clones, each producing one kind of antibody, has been estimated for humans as 10^7 to 5×10^7 [44]. For small tadpoles the number is 10^5 [71].

Using no more than some basic assumptions about the size of recognition sites and some reliability theory, Perelson and Oster[71] have analyzed 'minimal antibody repertoire size and reliability of self-non-self-descrimination'. They come to the conclusion that the lower limit of the repertoire size is around 10^5: below this number a lymphocyte system could not cope with all potential antibodies and function reliably. For an upper limit Perelson and Oster show that repertoire sizes of 10^6–10^7 are fully sufficient. These figures are derived from assumptions about the size of the recognition site of antibody molecules and from logistic requirements alone and are valid

for all species with antibody-producing monospecific lymphocytes.

If all possible pathogens are equally probable to attack, then the 'standing armies' that can be maintained to absorb the initial attack are limited to 10^4–10^5 cells, as we pointed out before. Or in other words: The organism cannot maintain 10^7 different standing armies of large size (the number of lymphocyte clones producing different kinds of immunoglobulins). One could object that the actual number of infectious diseases that afflict man is much smaller than 10^7. Why hasn't man evolved hereditary immunity against the diseases that actually afflict him, rather that keeping clones against millions of potential diseases, most of which don't exist or have ever existed? If a species would concentrate on maintaining lymphocyte clones against the few hundred or thousand infectious diseases that actually occur, then it could raise the threshold of infectivity – the size of the inoculum required to produce disease – correspondingly. Since infectious diseases greatly reduce the fitness of afflicted individuals, one would expect the human species to have evolved hereditary immunity. There appears to be a paradox.

The apparent paradox of the maintenance of defenses against nonexisting diseases can easily be resolved if one takes into consideration the speed at which new pathogens can evolve. An illustrative example is the influenza virus which causes world wide flu epidemics in man. After a pandemic (such as the worldwide flu epidemic in 1919 which claimed millions of lives), there is widespread immunity, preventing further infections. The worldwide immunity reduces the flu virus to very low residual levels. Nevertheless, in the course of a few years, a new worldwide flu epidemic appears. What happens is that the flu virus changes its antigenic characteristics to such an extent that the existing immunity (from the previous epidemic) is no longer effective. In other words the standing army of flu specific lymphocytes (acquired after considerable suffering) cannot cope with the new flu virus. A new, specialized defensive clone is needed to combat the changed virus.

The flu virus is an extreme case: It is capable of major antigenic shifts within a few years. These shifts involve animal intermediate hosts ('swine flu') and unusual genetic recombination processes (comp. Kaplan and Webster[38]). In addition there is ordinary antigenic drift of the virus. Residual amounts of virus are attacked by people's immune system with an intensity that varies according to the antigenic characteristics of the virus. Therefore, mutants are selected that have altered characteristics. This antigenic drift is responsible for minor outbreaks of flu epidemics between the major pandemics every ten or twenty years, which are due to antigenic shifts (involving unusual genetic recombinations). Thus the flu virus can evolve significant antigenic changes well within a person's lifetime. This discrepancy in the speed of evolution is by no means unique to the flu virus.

The vertebrate immune defense system is a general purpose system: It can cope with all potential antigens, not only with already existing antigens. Without this capability to respond to ever novel antigens, it would be useless because of the speed with which new antigens evolve.

7. Antigen recognition depends upon recombination of MHC alleles from a polymorphic population

In the battle between pathogen and organism it is imperative that the organism be able to recognize the pathogen as such. Conversely, if a pathogen can avoid recognition, it will not be attacked by lymphocytes or inhibited by antibodies. Thus pathogens should camouflage themselves, taking on the characteristics of the organism's own cells.

Cercariae of *Schistosoma mansoni* use camouflage. After a cercarium penetrates the skin of its human (or mammalian) host, it sheds its tail (which is attacked by the immune system) and covers itself with glycoproteins from host cells[32], thus acquiring the 'self'-defining histocompatibility antigens of its host. Exempt from attack, the cercarium can travel to the host's liver without being destroyed. After finding and joining a mate, the cercarium develops into a schistosoma, capable of shedding hundreds of eggs a day for years. Cercariae are quite large in comparison with bacteria and rely on a complicated life cycle for the transmission of the disease (schistosomiasis) involving an intermediate host (snails). Fortunately, bacteria seem to be less capable of adopting this strategy of 'stealing' the host's self-defining tissue antigens. (For further details see the survey article by Bloom[9].)

Bacteria and viruses are small enough for airborn transmission from host to host, and they enjoy an advantage over larger parasites that do not reach new hosts in this way. However, they also carry less genetic information than cercariae or protozoan parasites. They do not play and probably are unable to play the complicated games of camouflage or sequential antigenic change that *Schistosoma mansoni* or *Plasmodium falciparum* (malaria) engage in.

Once inside a host, bacteria and viruses are subject to selective pressures from antibodies and T-cells. These pressures would drive them towards camouflage and indistinguishability from host cells if they would remain in the same host long enough or if the pressures in different hosts would be the same. The well studied shifts of influenza virus strains are due to the selective pressures from host antibodies[39]. Thus in a clone where individuals have identical 'self'-defining antigens, viruses, bacteria and fungi would evolve that would be indistinguishable from self and which could not be attacked by antibodies and by T cells.

Self-defining antigens thus must change from generation to generation and from individual to individual. The polymorphism of the MHC complex and the numerous alleles at the MHC loci are effectively randomized by sexual recombination. Proof of the effectiveness is the rejection of tissue transplants when recipient and donor are not homozygous twins. Even when donor and recipient are matched for MHC compatibility, rejection still takes place and immune suppressive drugs must be given. MHC alleles are approximately selectively neutral. Small, isolated populations would in the course of time lose selectively neutral alleles through drift. Bremermann[11] has proposed a mechanism of sperm selection in vertebrates that would enhance MHC diversity and which would counteract genetic drift. This mechanism

would be analogous to mechanisms of pollen selection in flowering plants[24]. *Existence of the conjectured mechanism still remains to be confirmed.* (The ill effects of genetic drift in small isolated human populations have been apparent in mountain villages in Europe prior to the onset of contemporary mobility and mixing. They can also be observed in the Nile valley where frequent first cousin marriages aggravate the effect. Genetic drift must have been a problem during much of hominid evolution when populations where small genetic drift seems to be a problem in rare species, like the cheetah, that survive in small numbers.)

8. Split genes, introns, exons, and enzyme variety

For a long time the generation of antibody diversity (more than 10^7 lymphocyte clones of different specificity) from a few germ line genes (comp. Watson[88]) remained a mystery. Then exons and introns and mRNA splicing were discovered and it was realized that variety is being generated by somatic recombination and sliding splice sites (comp. Alberts et al.[1]).

Split genes are the rule rather than the exception in eucaryotic cells and their function has remained somewhat of a puzzle. They have been recognized as sources of rapid generation of polymorphism. Craik et al.[22] (p. 1125) write: 'A comparison between eukaryotic gene sequences and protein sequences from homologous enzymes from bacterial and mammalian organisms shows that intron-exon junctions frequently coincide with variable surface loops of the protein structures' ... 'since intron-exon junctions map to protein surfaces, the alterations mediated by sliding of these junctions can be effected without disrupting the stability of the protein core' ... 'junctional sliding provides a means for diversification of genes. This important function may be one evolutionary reason for the existence of segmented genes.'

Just as in sexual recombination, the benefit for evolution in the long run cannot be the selective force that maintains the intron-exon mechanism. Instead the appearance of the splicing sites on the core of enzymes that leaves the cores of enzymes intact fits perfectly with our hypothesis that variety is a defense against the molecular intrusions of microparasites. Toxin binding sites would not be the same as the active sites of enzymes. Hence variation of the binding sites can throw off the parasites without interfering with enzyme function.

9. Conclusion

We have presented a theory of evolutionary stability of sexuality which identified three different circumstances that favor sexual reproduction over asexuality.

1) Recombination is a repair mechanism for microorganisms that live in temporally or spatially inhomogeneous environments.

2) Recombination in a polymorphic population is a source of diversity which confounds pathogen adaptation in gene-on-gene interactions.

3) Recombination in a polymorphic host population is a source of individuality with respect to 'self'-defining MHC allele combinations (diplotypes) that distinguish self from nonself in systemic immune defenses.

Proposal 1 could be tested in experiments with bacterial cultures, for example by shifting *E. coli* from a growth medium in which genes for lactose metabolism have been repressed to a medium rich in lactose. Proposal 2 also could be tested in cultures of bacteria and bacterial viruses (phages). Both *E. coli* and phages have been studied extensively since the early days of molecular biology and experiments could build upon this knowledge.

Diseases of crops and forests provide a natural laboratory for our theory. Assays of better discriminating power than electrophoretic methods should be developed for the study of polymorphism (or the lack of it) in natural and cultivated crops and forests. The genomes of pathogen strains could be sequenced, the conformations of their gene products determined, and differences between strains characterized, as has been done for some human viruses, notably the influenza virus. The gene-on-gene interaction of host proteins with corresponding parasite proteins could be studied. A better understanding of these interactions, their polymorphism, and their population dynamics could be important for the genetic management of crops and forests.

Proposal 3 could be tested in naturally occurring populations of parthenogenetic lizards and fish. Tissue typing could determine whether such populations are clones. Estimates of the time elapsed since becoming parthenogenetic would be important. Sexually reproducing but highly inbred populations of mice are equivalent to parthenogenetic clones. Susceptability of such populations to disease could be studied in the laboratory and compared with susceptability of wildtype mice. Here the theory of commensalism between host and parasite would have to be taken into account. Even if the hosts were to be defenseless and at the mercy of their parasites the latter still would have to be commensal.

Until the late 1970s genes, except for rare mutations, were assumed to be quite stable. The purported stablity was reflected in the models of mathematical genetics. Then transposable elements, introns and exons, mRNA splicing, sliding splice junctions, and gene conversion were discovered. New types of mathematical models are required.

10. New mathematical models

The newly discovered richness of processes causing genetic variability is too complex for realistic mathematical models of the molecular changes involved. Instead one can characterize alleles through their phenotypic effect on model parameters. (This approach is analogous to the game models of Maynard Smith[60], where the model parameters are values that determine game strategies. Mutations are treated as perturbations of these values.) Molecular processes generate breakthroughs from time to time: alleles that confer host resistance, a parasite allele that overcomes the resistance conferred by a specific host allele, or a new parasite allele that changes the trade-off between transmission rate and damage to the host.

We are thus led to models of host-parasite population dynamics that allow subpopulations of host and parasite strains carrying different alleles, which cause different values of the phenotypic parameters: birth and death rates, excess death rates, and strain specific transmission/

infection rates. New mutant strains cause perturbations in the system. The effect of perturbations can be studied: whether the mutant strain spreads or dies out, whether it comes to dominate, or coexists in a polymorphic equilibrium.

For an asexually reproducing host population Bremermann and Fiedler[16] have shown that a stable polymorphic equilibrium between hosts and parasites is possible, where each parasite strain regulates a corresponding host strain to a level below the carrying capacity of the environment and where the total population nevertheless approaches the carrying capacity. If a host strain appears that is resistant to all parasite strains it will drive susceptible hosts to low population levels till the corresponding parasite infections can no longer be sustained and die out. After this the host population remains polymorphic indefinitely, with the resistant strain dominating, unless resistance involves a cost in the form of a lower reproductive rate. Bremermann (unpublished) has recently extended these results to sexually reproducing host populations for the case of gene-on-gene resistance and recessive susceptibility.

The fate of parasite mutants that differ in their trade-off between transmission rate and damage to the host have been modeled by Bremermann and Thieme[15]. If hosts are susceptible to all strains but infection by one strain precludes a simultaneous infection by another, then asymptotically all strains die out except those that maximize the basic reproductive rate of the parasite (as defined by Anderson and May[5]). This corroborates a static optimization argument by Bremermann and Pickering[14] and is a special case of a game-theoretical optimization model.

Game-theoretical models of populations where mutants affect strategy parameters have provided many insights (comp. Stearns[79], Maynard Smith[60]). Host-parasite interactions can be viewed as games, where each player optimizes (through mutants) its own fitness. Game theory then yields criteria for optimal strategies such as the Nash equilibrium in noncooperative games (comp. Bremermann and Pickering[14]).

Optimal strategies, however, do not always correspond to dynamic population equilibria. The pay-off in these population games is in terms of increased or decreased subpopulations whose alleles determine the strategies which they play. The game models thus are imbedded in dynamic population models. In other words, game models are simplifications of the type of models described above, where mutant strains may invade the population. Optimal game strategies may be easier to compute than dynamic equilibria. Sufficient conditions for optimal game strategies to be locally stable dynamic equilibria have been given by Maynard Smith[60] (Evolutionarily Stable Strategies' – ESS for short).

In the models of Bremermann and Fiedler[16] and Bremermann and Thieme[15] the game approximation was not necessary. In Bremermann and Pickering[14], however, the full dynamic description would have been so complex as to be intractible. Here the game-theoretical formulation is used as a simplification. It predicts the breakdown of host-parasite commensalism under certain conditions. In a forthcoming paper (Bremermann, unpublished) it will be shown how such a breakdown may be responsible for the high mortality that is associated with AIDS.

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